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Cover picture: "Sara Begum, center, at her home next to her husband and daughter in Kashmir, last month". New York Times, under the news heading: "Kashmir, Under Siege and Lockdown, Faces a Mental Health Crisis"

Identifying depression symptoms among general population living in conflict zone in Jammu and Kashmir

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Editorial

This issue has a variety of papers from Japan, Saudi Arabia, Pakistan, Qatar, Kuwait, Turkey, Iran, Australia and Lebanon.

Kelendar H et al., used a descriptive exploratory approach in the modality of a case study through semi-structured interviews with thirteen staff involved in the care of PWT2D in four Kuwaiti primary healthcare centres. The aim is to map the flow of patients with type 2 diabetes (PWT2D) without any complications in primary care, identify potential waste and make recommendations for improvement. Staff acknowledged waste as non-standardised clinical practice, delays, waiting times and unnecessary patient visits. Four potential improvements were identified which could be consolidated into a single visit: using point of care testing, the posting of laboratory results to GP computer systems, the introduction of guidelines that standardise the practice for the patient's visit and permitting the GP to prescribe four months of medication. The authors concluded that the process map of PWT2D has highlighted waste and improvement suggestions that may reduce workload, enhance patient satisfaction, avoid unnecessary visits, enhance the timeliness of laboratory testing, improve communication between and across departments and minimise use of resources without undermining the quality of care. These suggestions need to be implemented and rigorously evaluated.

Miki, E et al., reported on the Effects of Touch and Massage Care in Advanced Alzheimer Patient. The patient was a woman in her late 80s with the most severe level of care need and dementia due to AD. Once a month during 5 months, unscented jojoba oil was applied to the patient's hands while she was seated on a wheelchair with her hands on a table, and she received 10 minutes of touch and massage care on each hand, for a total of 20 minutes. Salivary amylase activity was measured just before and immediately after every intervention session as a non-invasive indicator which reflects psychological stress. The average salivary amylase values before and after the 5 times that the patient received the touch and massage care were 185.6 KIU/L (SD = 44.5) and 112.8 KIU/L (SD = 38.3), respectively. A significant decrease was observed (P = 0.043). As for the patient's appearance during the sessions, when she was helped to move her arms onto the tabletop, her arms and legs sometimes stiffened, and she flexed them intermittently, however, the stiffening diminished after the massage began. The authors concluded that since this was a pilot case study with a single patient, the results cannot be generalized. However, the study showed that touch and massage care could provide pleasant stimulation for an advanced AD patient with verbal communication difficulties and offered the possibility of reducing physical and emotional stress; therefore, it provides important clues for the future occupational therapy intervention and care of advanced AD patients.

Al Saudi H et al., surveyed primary care physicians about their comprehension of HBA1C , and their understanding of the common medical conditions that can affect the accuracy of HBA1C. Although the test is simple and straightforward, but not, in reality health care professionals needs to be very vigilant and critical when interpreting values of HBA1C as HBA1C is affected by many other medical conditions and medications, and most of these medical conditions co -exits with Diabetes melilites or develop as a result of diabetes itself.

In this research we did a cross sectional study among family physicians working in primary health care corporation Doha, Qatar to see the awareness and understanding of the different medical conditions that can affect the accuracy of HBA1C levels and to see if the physicians are aware of any alternative bio marker other than HBA1C,that is reliable in conditions in which HBA1C could not be accurately used.

Hussain & Nizamani conducted a cross sectional study, gathering total number of patients registered with T2DM at AbuNakhla health center, Doha, Qatar. The study aims at looking at the prevalence of T2DM in a small rural population of AbuNakhla, Doha, Qatar with age and gender distribution. The results showed high disease burden in local population of AbuNakhla. Around 51% patients with T2DM are under the age of 50 years, out of which 10% are under the age of 35 years. Also, the number of females with T2DM is quite high under the age of 35 years. Around 49% patients are above the age of 50 years. The authors concluded that there is a high diabetes prevalence in AbunAkhla, Doha Qatar. Prevalence is higher in younger age group i.e under 50 years with a rapid rise in prevalence in age group 36 to 50 years for both males and females.

Dr AlKhaldi Y. M did a cross sectional study to explore the prevalence of depression and anxiety among tourists in Asser region, KSA. The mean age of the participants was 31±12.5 years, women represented 56%, and 53% were married. More than one two-third (61%) complained of physical symptoms, i.e. chronic headache (14%), chronic joint pain (12%), IBS (10%), and chronic back pain (9%). More than two-thirds had depression (68.9%), (59.5%) have GAD, while both disorders affect (28.4%). Mild depression affects(30.4%), moderate depression (19.8%), while severe depression reported among (18.7%). Moderate to severe anxiety were more in women (30.3%) compared to men (20.9%) with a significant difference (p-value = 0.018).

Dr. Jamal, et al, conducted a cross sectional study, conducted among medical students, trainee and resident doctors of Jinnah Sindh Medical University and Jinnah Postgraduate Medical Centre respectively from July 2019 to December 2019. The aim was to assess the knowledge, attitude and practices regarding stethoscope disinfection among students, trainee and residents doctors at Jinnah Postgraduate Medical Center. Their study concluded that there is a lack of practice by medical providers to disinfect their stethoscope in spite of considering stethoscope as potential vector for nosocomial infection. Therefore measures should be taken to elevate practice of stethoscope disinfection to reduce the nosocomial infection effectively.

Alshahrani A.S, reported a rare presentation of ATIL with hepatitis for a woman who has Crohn's disease and was treated with infliximab for 9 months. She had clinical and biochemical improvement after discontinuation of infliximab and starting steroid therapy. The authors concluded that treatment with Infliximab may cause a lupus-like syndrome, which can be reversed upon its discontinuation.

Khan, H., et ., attempted to quantitatively analyze the impact of type of contact and duration of contact with infectivity of novel corona virus. They analyzed 378 suspects/cases to prove our null hypothesis. Relevant information's were recorded on a predesigned proforma prepared in accordance with the objective of the study in SPSS. History of contact with positive COVID-19 patients was contributing in 35/41(85.36%) confirmed cases. We observed that 25/41(60.97%) of the positive cases had a contact history > 5 days. The authors concluded that it is the duration of contact and not the type of contact that has a statistically significant correlation and a higher probability of exposure to COVID-19.

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Lean processes mapping of diabetic patient flow in primary healthcare centres in Kuwait highlights opportunities for fewer patient visits

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Abstract

Background: Healthcare systems are facing the ever-present challenges of increasing demand and limited resources. To address these concerns, some healthcare systems have adopted lean methodology specifically to enhance patient flow by eliminating waste in hospital settings. Little is known about the use of lean in the primary care setting: a setting that consumes considerable resources and increasingly handles chronic diseases such as diabetes.

Aim: To map the flow of patients with type 2 diabetes (PWT2D) without any complications in primary care, identify potential waste and make recommendations for improvement.

Methodology: We used a descriptive exploratory approach in the modality of a case study through semi-structured interviews with thirteen staff involved in the care of PWT2D in four Kuwaiti primary healthcare centres.

Result: PWT2D typically visit their General Practitioner (GP) at least every two months for a review appointment. When a blood test is required to monitor blood sugar levels, three more visits are required, involving the blood test, collection of test results by the patient and a review of these results with the GP. Staff acknowledged waste as non-standardised clinical practice, delays, waiting times and unnecessary patient visits. Four potential improvements were identified which could be consolidated into a single visit: using point of care testing, the posting of laboratory results to GP computer systems, the introduction of guidelines that standardise the practice for the patient's visit and permitting the GP to prescribe four months of medication.

Conclusion: The process map of PWT2D has highlighted waste and improvement suggestions that may reduce workload, enhance patient satisfaction, avoid unnecessary visits, enhance the timeliness of laboratory testing, improve communication between and across departments and minimise use of resources without undermining the quality of care. These suggestions need to be implemented and rigorously evaluated.

Key words: Lean, process mapping, patient flow, value stream mapping, efficiency, hospital, healthcare

Background

Healthcare systems are facing the challenges of rising demand and limited resources [1]. This increase is due to an ageing population, sedentary lifestyle and increased non-communicable disease burden [1, 2]. Healthcare organisations are looking to make better use of available resources and avoid waste. A wide range of waste types with distinct characteristics and classifications have been highlighted in healthcare [3]. To address these challenges, several methods have been advocated [4, 5] including lean methodology [5].

Lean is a widely-used method that originates from Toyota, a Japanese car manufacturer and was first introduced to the public domain by the book, The Machine that Changed the World [6]. The central insight of lean is to understand how we can maximise our resource efficiency [7]. It consists of a series of structured problem-solving tools [8]. Process mapping, also known as value stream mapping (VSM), is one of the most common lean tools applied in healthcare, aiming to visualise all activities of patient flow [9]. Fillingham mentions that in most processes, non-added value (NAV) steps account for nine times more effort than AV steps [10]. Typically, lean begins with mapping the patient flow in order to identify delays, repeated visits, waiting times, inappropriate procedures and errors [11]. Poor patient flow leads to increased healthcare costs, an increase in the likelihood of errors, reduces healthcare service efficiency and results in both patient and staff dissatisfaction [7]. Process maps can be used to redesign the patient's journey [12] by eliminating, combining, rearranging and simplifying (ECRS) the stages of patient flow [13]. Using VSM across different healthcare systems and among a variety of specialties shows encouraging results and benefits [14-16]. Much of the reported use of lean in healthcare has focused on patient flow in hospitals in developed countries [17]. Less is known about the potential of lean in developing countries [18], especially primary care settings [19, 20]. Additionally, a systematic review of the use of lean in healthcare concluded that lean interventions have a positive yet inconsistent benefit on patient flow that calls for more research [21]. In this paper we focus on the use of lean process mapping to describe the flow of patients with type 2 diabetes (PWT2D) in Primary Healthcare Centres (PHCs) in Kuwait.

Diabetes is at the top of the list of non-communicable chronic diseases in Kuwait. Diabetes effects 24% of the Kuwaiti population which is considered to hold the sixth-highest prevalence of diabetes in the world [22]. As a result, diabetes is the principal or secondary diagnosis in 40.6% of hospitalisations in Kuwait [23]. The majority of PWT2D in Kuwait were registered at a PHC [24]. The efficient use of primary care resources to manage diabetes is an important challenge.

Method

This is a descriptive exploratory qualitative study carried out via interviews attempting to capture the current process map and elicit potential improvements.

1-Setting

The Kuwait healthcare system is highly centralised with the Ministry of Health (MOH) being the national body that oversees the system across the country [25]. In 2015, the MOH had 94 PHC covering six healthcare regions [24]. This case study is based in the Hawalli region, which has the highest primary healthcare population per primary healthcare centre (PHC) (n = 62,652) [24, 26]. The Hawalli population accounts for almost one million people, where the annual number of visits to diabetic clinics is 200,044. Both numbers represent 20% of their totals for Kuwait [24, 26]. A convenience sample of four PHCs was selected on a voluntary basis.

2- Participants

The interviews included at least one staff member from each department involved in the flow of PWT2D without complications or comorbidities, including physicians, nurses, pharmacists, lab technicians and workers in different administrative positions. The selection of participants was done through consultation with the PHC director. The heads of departments were also interviewed. All participants consented to participate but did not consent to audio recording of the interview.

3- Date collection process

The interviews took place at the PHC (in the office or a meeting room) in the form of 'one-to-one', 'face-to-face' for a maximum of one hour. To understand the current process map for PWT2D, the researcher asked the healthcare workers (HCWs) to describe how patient services are provided in practice, the personnel involved at each step and the estimated time needed for completion. Furthermore, attention was also given to waiting times, waste, problems within the steps and ideas for eliminating or reducing these issues. The following fifteen questions were used in the semi-structured interview:

Questions to understand the current process map for PWT2D

1. How many steps are there in the flow of PWT2D from one appointment to another appointment?
2. How many times is the patient passed from one person to another (hand-off)?
3. What is the approximate time taken for each step (task time)?
4. What is the approximate time between each step (wait time)?
5. What is the approximate time between the first and the last step?
6. Does the patient join a queue or is put on a waiting list?
7. Are there any delays which occur on a regular basis?
8. How many steps add no value for the patient? Adopted from [29]

Questions to identify proposed corrective action
1. Where are there main problems for patients or staff?
2. Is there anything that will hinder the process?
3. Is the patient getting the most appropriate care from the appropriate person?
4. Is the care being given at the most appropriate time and in the ideal place?
5. Are there procedures that could be done in the same visit?
6. Could the patient have several investigations at the same visit?
7. Could patients carry their own records? Adopted from [29]

During the interview, the researcher took extensive notes by hand and at the conclusion of the interview, read them back to the participant to review and clarify any inaccurate statements or missing information. Aside from interviews, the researcher also reviewed the existing design artefacts (such as layouts and drawings), relevant process statistics (such as activity volume and frequency, the number of PWT2D visits annually and other relevant statistics when available) and observed/followed a patient process map.

3- Data analysis
For qualitative data analysis of the answers obtained, all information was transcribed and categorised. The impact of the proposed changes was evaluated using different measures including turnover time, the length of the patient journey, number of visits per year, the total number of steps and patient satisfaction.

4- Drawing the process map of PWT2D
In order to capture an accurate representation of the process as opposed to the assumed occurrences, the current process was mapped. Based on interviews, all the steps and processes required for providing the services for PWT2D were mapped out. The final version of the process map was presented to the participants for waste identification and potential improvement suggestions. The ECRS framework was used to guide the process of creating corrective actions, thoughts and ideas.

5- Lean principles and tools used throughout the case study
Table 1 shows the lean principles and tools used throughout this case study.

6- Ethical Approval
This study was ethically approved by the Kuwait MOH ethics committee. Approval was also granted by the Chair of the Humanities, Social and Health Sciences Research Ethics Panel at the University of Bradford. Verbal consent was obtained from all participants throughout the research and their identities will remain anonymous. Participation was optional.

Results

Across four PHC sites in Kuwait, thirteen staff members were interviewed. The minimum number of annual visits to the general practitioner (GP) for PWT2D was considered. Furthermore, only the typical process map for PWT2D from one appointment (undergoing a lab test which usually includes a HbA1C test) to the next appointment was drawn up.

1-Annual visits to the GP for a patient with controlled diabetes
The minimum number of annual visits to the GP for a PWT2D were six visits (Figure 1).

The reason for the results in Figure 1 is the limitation set out by Kuwait MOH instructions, only permitting GPs to prescribe two months' worth of medication for PWT2D at a time. The patient is required to see the GP every second month in order to review and renew their medication.

Table 1: Lean principles and tools used throughout the case study

LEAN PRINCIPLES AND TOOLS USED THROUGHOUT THE CASE STUDY
Just in time production
ECRS
Standardised work
Gemba walk (direct observation of the workplace)
Waste elimination
A3
Flow improvement
VSM
Current situation analysis
Employee involvement
Lead time reduction
Patient involvement

2-Current process map

The patient journey started with arrival at the PHC, before proceeding to sign-in at the reception where the patient received a number. They took the random finger prick blood sugar test with the nurse and then waited in the waiting area to be seen by the GP who saw the patient and wrote the prescription and the lab request. The patient would then go to the pharmacy to collect medications and to the lab to give a blood sample. Once the lab results were available (usually a few days/weeks later), the patient would receive them and bring them to the next GP consultation visit. In a typical follow-up consultation for PWT2D, the GP reviewed the patient's lab results, specifically the HbA1c test and recommended an adjustment in medication accordingly. This simple service provided by the healthcare sector travels through multiple steps where different flows are branched onto different stream paths. Based on the interviews, the researcher drew up the current process map for PWT2D (Figure 2).

When the practitioner requested a lab test, excess time was spent by the patient on transport, testing, waiting, collecting and consulting the GP for the lab results. Based on the current process map, the delay is directly apparent. Patients were required to do blood tests in a separate location and wait for the results. Once the results became available, the patient was required to collect them and bring them to the next appointment. Within this process is a sample flow map that is beyond the scope of this case study. Due to the lack of networking and inter-department communication, additional steps and pathways are necessary to transfer lab information. Several paths were identified within the four PHCs, but only the common path for a patient with a lab request was considered.

3-System deficiencies and the proposed corrective actions

Most of the interviewed HCWs across the four PHCs reported that the practice of lean principles empowered them to identify the obstacles within the healthcare system and explore improvement opportunities. Based on the observation phase and with the help of interviewer feedback on the current process map, multiple improvement opportunities were determined.

One of the findings was the lack of a formal standardised process for different steps within the flow of PWT2D. For example, when GPs were asked about the guidelines for the number of times PWT2D should be seen annually and the frequency of required lab investigations, varying responses were received. One participant said that their response depended upon the patient's condition and whether the patient was 'controlled' or 'uncontrolled'. Another GP mentioned that the patient is seen once the lab result finished. After reviewing the existing records, it was determined that

Figure 1: The minimum number of annual visits to the GP for a patient with controlled diabetes

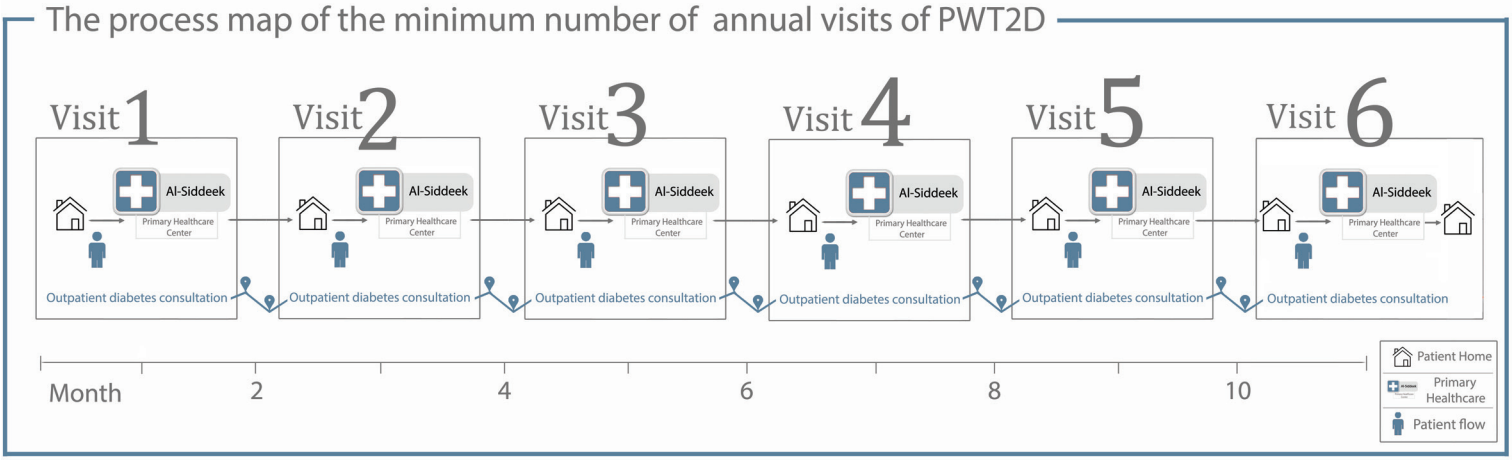

Figure 2: The typical process map for PWT2D detailing the steps from one appointment (undergoing a lab test which usually includes a HbA1C test) to the next appointment.

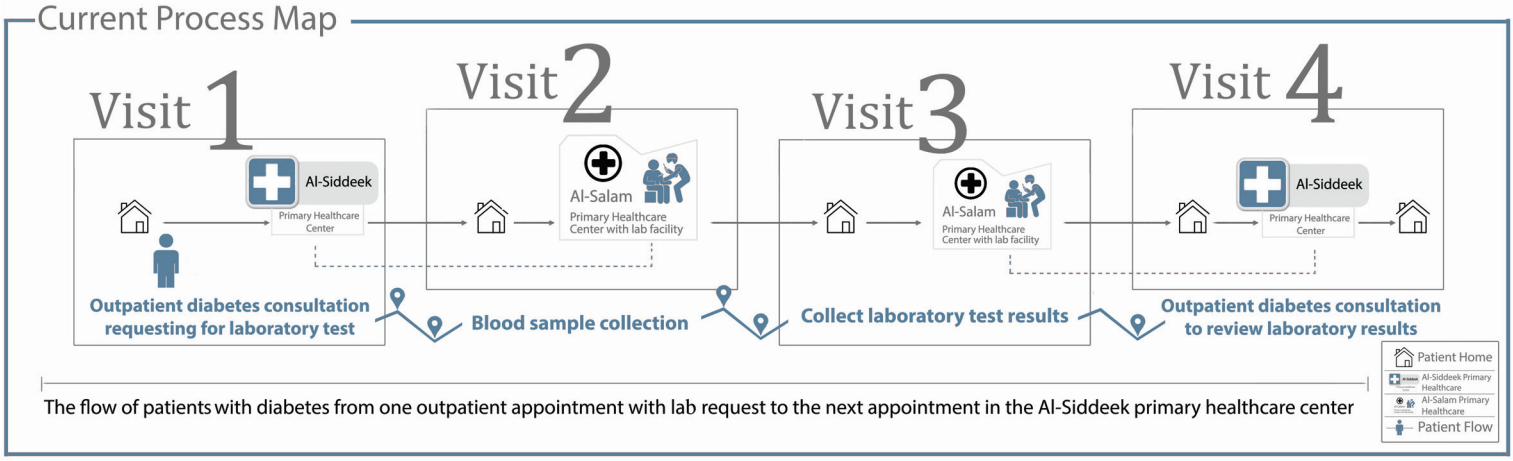

Table 2: Suggestions for improving the flow of PWT2D with the expected benefits for the patient and organisation

	The Process	Current Situation	Target Situation	Proposed Corrective Action	Potential benefits to the Organisation	Potential benefits to the Patient
PWT2D annual visits						
1	Reduce the annual visits to the GP for PWT2D	Minimum six visits annually	Three visits annually	A new policy allows GP to prescribe medications for 4 months or provide to patients necessitating GP visit	Appointment slots will be freed up and total annual visits could be reduced by 50%	Greater satisfaction due to elimination of unnecessary visits as average total visits per patient could reach three per year
2	Reduces the interval between patient visits	No informative guidance for patient visits	Informative approach guiding patient visit	Introduce guidelines that standardise the practice	Clearer and more informative practice	Patient satisfaction is increased due to removing unnecessary visits
PWT2D from one appointment (with lab test which usually includes HbA1C test) to the next appointment						
1	HbA1c test process time reduction	10 days	30 minutes	Point of care testing	Lowers workload and frees up appointment slots	Patient satisfaction increases due to minimising visits from 4 to 1
2	Reduces patient waiting time for next appointment	14 days	On the same visit	Point of care testing	Combine two appointments together	Patient satisfaction increases due to reduced waiting time
3	Reduces the time between blood sample and result availability	7 days	3 days	Lab and doctor electronic system connection	Minimise waste, errors and delays	Patient satisfaction increase due to not needing to travel for results

PWT2D are required to visit the GP at least once every two months due to the limitations of the medication prescription that must be renewed every two months.

The other finding was that no automated process exists to obtain the lab results. As a result, the patient is required to conduct further visits to various locations for both the providing of blood samples and the collection of results. (This is the case in those PHCs that do not have lab facilities). When one patient was asked for her thoughts on the process, she revealed she was frustrated at being required to travel to another location to provide a blood sample and then being asked to return later for the results. She questioned why it was not possible for the results to be sent directly to her file. She also mentioned that one of her relatives on follow up in another PHC was not required to do all these steps as this second PHC had the lab facilities required. It is worth noting that an electronic system is available and is used by the GPs, but that this system is not connected to the lab department. Moreover, there were several complaints from GPs about the current electronic systems that, if resolved, would result in significant time-savings for GPs to spend on the patient without interruption. Another solution that has the potential to improve this situation is a establishing a point of care testing (POT) for the HbA1c. POT combine the process steps by having the follow-up investigations carried out on the same visits where the results are available immediately and can be easily reviewed by the GPs. Based on participants interviews, Table 2 summarises some of the preliminary suggestions for improving the flow of PWT2D with the expected benefits for the patient and the organisation.

All the proposed corrective actions aim to enhance the patient visit flow and target improving the healthcare system efficiency, which will lead to better access, higher quality of care and reduced costs.

Discussion

The results of this study show that lean management can play a significant role in optimising the flow of PWT2D (without complications) in PHCs in Kuwait where a number of improvement opportunities were discovered. To the best of the authors' knowledge, this is the first process map describing the flow of PWT2D within PHCs from one appointment to another. Discussing the flow of PWT2D through the current process map enhanced HCWs' learning, especially in the identification of waste and inefficiencies and suggesting priorities for changes. Several opportunities for improvement were identified to mitigate waste and inefficiencies in the flow of PWT2D.
One opportunity for improvement is providing lab results as soon as possible. This could be achieved by using an IT-based system instead of a paper-based system, with the lab computer system connecting directly to GP computers, removing the need for the patient to collect their results and bring them for their next visit. The integrated computer health information system could help improve user management and increase patient flow efficiency. This is reflected in the delay in management plans, patient frustration and waste of resources. Moreover, each additional step in the process provides further opportunity for the introduction of errors, leading to safety concerns. Arguably, a better solution is providing a POT that will include the lab work and results in the patient's original appointment. A POT will improve the timeliness and accuracy of the result, reduce HbA1c test process from 10 days to 30 minutes, condense patient waiting time for next appointment from 14 days to the same visit and consequently reduce the annual number of patient visits.

Another improvement opportunity is providing standardised clinical, policy and procedure practices. In lean, standardised processes are an important aspect in achieving a highly efficient system [27]. Lack of practice standardisation is a common finding of process maps in various services[28]. In this study, asking different physicians about the guidelines for the average number of times PWT2D were required to be seen annually and the frequency of necessary lab investigations returned a variety of responses. For example, in response to the question on the frequency of HbA1c measuring, two answers were every three months, another answer was depending on the case and one GP simply said, 'I am following the NICE guideline'. As a consequence, it is highly recommended to have a guideline appropriately implemented. Another important finding was that the patient was required to visit the GP once every two months for renewal of medication regardless of whether the patient's diabetes was classified as controlled or not. This could be improved if the administrative policy allowed GPs to prescribe the medication for four months or for patients to obtain the medication without necessitating a GP visit.

The findings regarding the direct time spent with the patient are consistent with previous studies. O'Leary et al. found in their research that hospitals spent most of their time on NAV activity for the patient [29]. As time spent on communication is significant, developing a system that maintains an efficient method of communication is a must. The lag in communicating lab results, inefficient patient-doctor communication and inherently fragmented systems are all potential contributors to delays, medical errors and poor quality of service. This aggravates the frustration patients will face during the journey of receiving healthcare services, as they often have to wait at each stage of the process and go through numerous steps. Reflecting on the previous recommendations with the consideration of the total diabetic outpatient visits, total annual visits could be reduced by 50% where average total of visits per patient could reach three per year. As a consequence of reducing the total number of visits, appointment slots will be freed up to allow more patients and reduce waiting lists, and provide the opportunity for GPs to spend more time with their patients.

The authors observed that by adapting VSM, employees receive guidance on how their work contributes to the flow of PWT2D, which increases understanding of the work of other professional groups and leads to greater application

of knowledge. This observation was also mentioned by Drotez and Poksinska [30] and by Rossum et al. [31]. Interviewed participants were also introduced to diverse lean strategies in order to maximise value and minimise waste. These included performing root cause analysis to identify waste, redesigning processes through the VSM tool, reducing variation in practice through the use of standard work and simplifying organisation operations to streamline patient flow. Another revelation from this research was the necessity of HCW engagement in the research project and the improvement initiative. Melanson et al. highlight the importance of teamwork as a critical factor for the successful implementation of lean [32].

This research provides several significant lessons to those interested in process mapping. Process mapping considers an innovative approach in Kuwait's PHCs that allows HCWs from different specialties to improve the patient flow and in doing so, the system efficiency. It offers leaders strategic recommendations that have the potential to improve the flow of PWT2D. It led to an understanding of the current processes, identifying areas for improvement and suggesting necessary changes. The full potential of the lean method can be achieved if it is implemented holistically, where lean becomes embedded within daily healthcare activities.

Conclusion

This case study contributes a practical example of how a lean-inspired approach using VSM or process mapping can be utilised in Kuwait PHC. It was carried out with the participation of HCWs to draw the process map of PWT2D. This facilitated the identification of the gaps in the system (different kinds of wastes), proposed solutions and measured the anticipated effect. The improvement could be achieved by eliminating immediately, where possible, NAV steps or combining multiple steps into one, mainly when steps cannot be eliminated. Additionally, processes could be rearranged and simplified where time, effort and cost could be saved. VSM is a promising instrument for PHCs in Kuwait, but the extent to which suggested changes can be successfully implemented remains to be seen.

Proposals for further research

A shortage of examples of lean application in PHC is noted. Therefore, this study is presented as one of the few examples of this theme; it should be considered a good contribution to the continuity of the research. To be able to draw more generalising conclusions, the majority of studies of this kind should be carried out in other departments within healthcare systems. In lean, the patient is at the centre of healthcare, so the HCWs should aim to understand value from the patient's perspective. Further research on in-depth patient involvement is recommended. In terms of method, further research should be carried out by supplementing interviews with observations or with a quantitative method.

Limitations

Our study was limited to PHCs from one healthcare area. Even though other PHCs in different healthcare areas have the same setting with similar processes and procedures, we cannot be sure that other PHCs face similar challenges. Another limitation was that interviews were conducted with a limited number of people based on availability. Thus, generalisations cannot be made for other groups based on the single group that has been investigated. However, this study allows understanding of the operational process of how one lean-inspired project can be implemented to improve system efficiency. Finally, the suggestions for improvement described in the context of this research work have not been tested.

Conflicts of interest

The authors declare no conflicts of interest.

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This research is a part of a larger study conducted by the principal researcher to achieve his Ph.D. degree at the University of Bradford. He is currently a full-time Ph.D. student sponsored by the Kuwait Ministry of Health through the Kuwait Cultural Bureau in London.

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Survey of primary care physicians about their comprehension of HBA1C, and their understanding of the common medical conditions that can affect the accuracy of HBA1C

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Abstract

Haemoglobin is a red blood cell protein, and the free glucose in blood tends to bind to this protein. This process is known as “glycosylation”; the result of this binding is HBA1C, or glycated haemoglobin. HBA1C measures the amount of sugar bound to haemoglobin (1).

As the life span of a red blood cell is 2-3 months HBA1C is checked every 3 months for monitoring of diabetes(2).

Hba1c does not only give us a decisive and dependable measurement of chronic hyperglycaemia but is also a good indicator of long term complications in type 2 diabetes mellitus (3).

This would seem simple and straightforward, but in reality health care professionals need to be very vigilant and critical when interpreting values of HBA1C as HBA1C is affected by many other medical conditions and medications, and most of these medical conditions co-exist with Diabetes mellitus or develop as a result of diabetes itself.

In this research we did a cross sectional study among family physicians working in the Primary Health Care Corporation, Doha, Qatar to see the awareness and understanding of the different medical conditions that can affect the accuracy of HBA1C levels and to see if the physicians are aware of any alternative bio marker other than HBA1C,that is reliable in conditions in which HBA1C cannot be accurately used.

Key words: primary care physicians, HBA1C, Qatar

Introduction

This is a cross sectional study that was conducted among fifty family physicians working in Primary Health Care Corporation, Doha, Qatar as family physicians are very commonly involved in diagnosis, management and follow up of patients suffering from type 2 diabetes mellitus.

The main aim of this study was to find out the depth of understanding and comprehension of HBA1C by primary health care physicians.

(1) If physicians were confident to diagnose type 2 diabetes mellitus based on values of HBA1C,
(2) If physicians were aware of different medical conditions and medications that can affect the accuracy of HBA1C,
(3) If physicians are aware of an alternative bio marker to HBA1C.

The physicians involved were both male and female and all of them had post graduate diploma or degree from their respective countries, in primary care.

The results from the study are shown below in the table and graphs and are quite interesting.

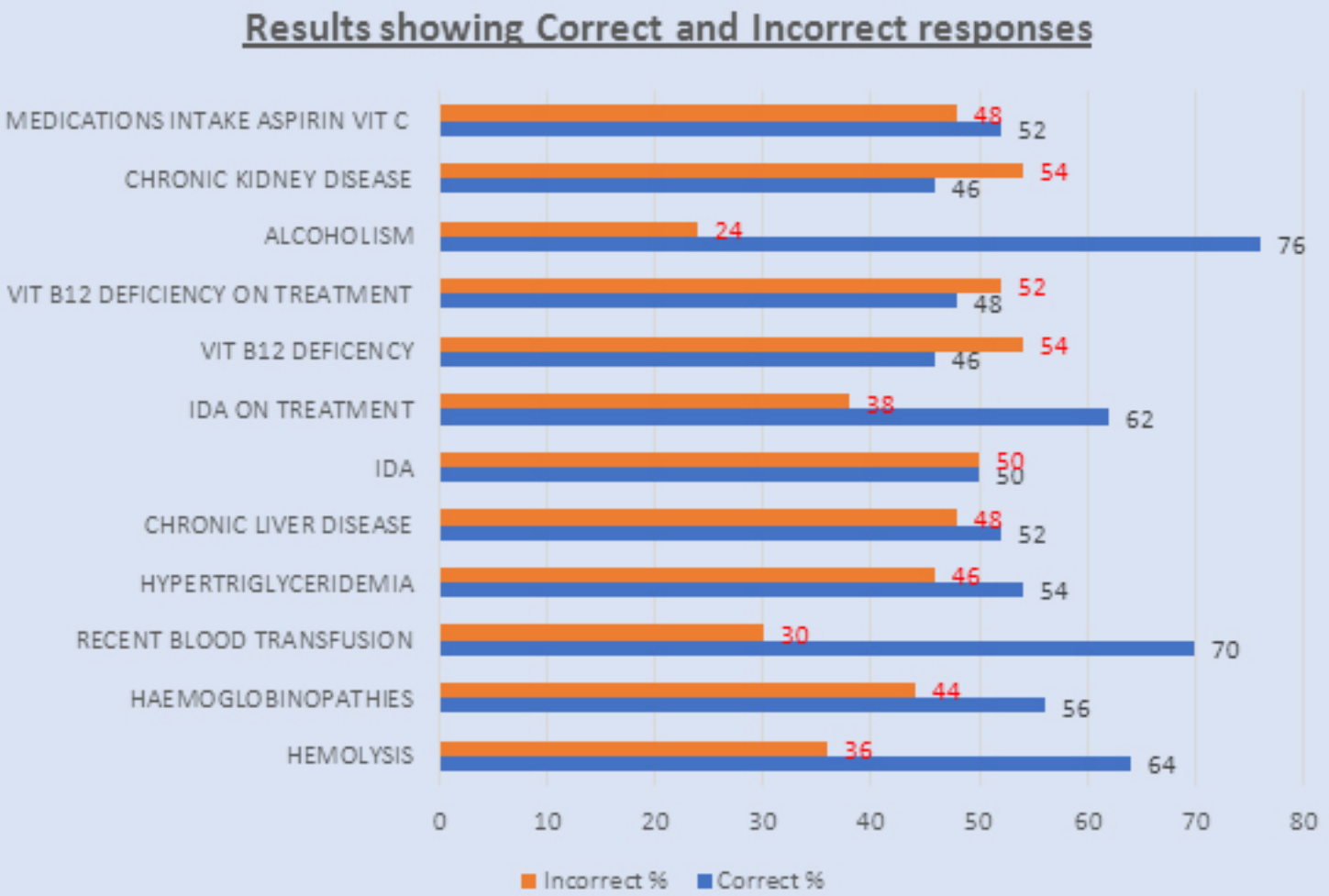
Figure 1: Answers to Basic Questions Showing Family Physicians Confidence in Dealing with Type 2 Diabetes Mellitus

Questions	YES IN %	NO IN %
Are you a practicing family physician	100	0
Are you confident: to interpret hba1c results	100	0
to make diagnosis based on hba1c	100	0
manage type 2 diabetes mellitus	100	0
diagnosis and management of pre-diabetes	100	0

Figure 2: Shows the Different Conditions that can Affect the HBA1C and the Percentage of Correct and Incorrect Answers by the Family Physicians

Effect On Hba1c	Correct Answers in %	Incorrect Answers in %
Hemolysis	64	36
Haemoglobinopathies	56	44
Recent Blood Transfusion	70	30
Hypertriglyceridemia	54	46
Chronic Liver Disease	60	40
Iron Deficiency Anaemia	50	50
Treatment of IDA with Iron	62	38
Vit B12 Deficiency	46	54
Vit B12 Deficiency Treatment	48	52
Alcoholism	76	24
Chronic Kidney Disease	46	54
Intake Aspirin	52	48
Awareness Of Alternative Biomarker To Hba1c	20	80

Figure 3: Shows the Correct Answers in Blue and Incorrect Answers in Orange as Percentage



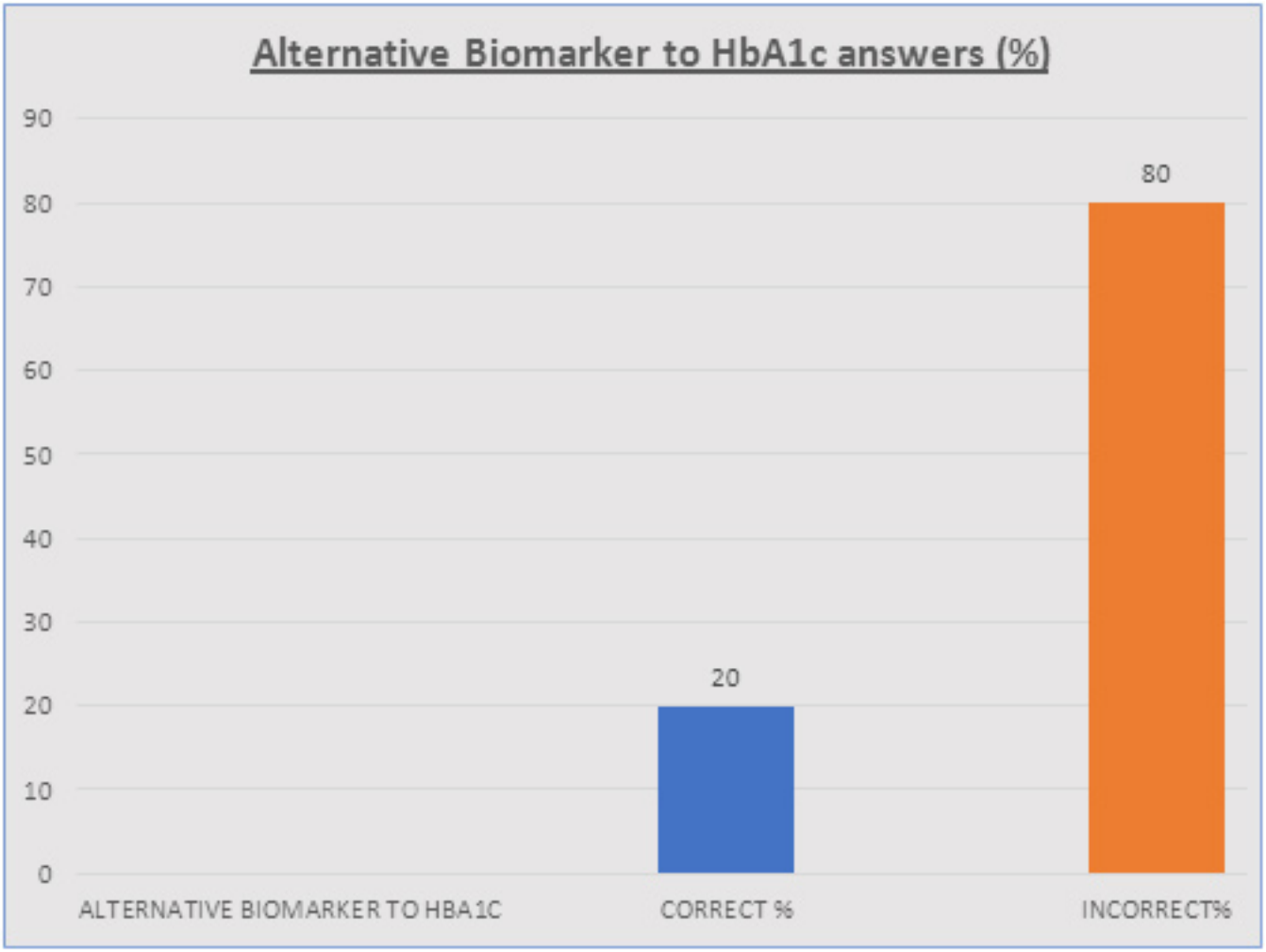
As obvious from data above all family physicians were confident that they can interpret HBA1C readings to diagnose and manage type 2 diabetes mellitus (FIGURE 1), but when asked in depth about different medical conditions that can interfere with validity and accuracy of HBA1C there were many incorrect answers (FIGURE 2).

As very obvious from data above there is a marked percentage of wrong answers, even against common conditions such as iron deficiency anaemia, vitamin b12 deficiency chronic kidney disease etc. (FIGURES 2, 3).

This clearly indicates that the physicians involved in the management of type 2 diabetes mellitus and interpretation of HBA1C results, are clearly not aware of how different medical conditions and commonly used medications can affect its accuracy and hence this can affect the entire management of type 2 diabetes mellitus in these patients. Keeping in mind that in patients with type 2 diabetes mellitus, conditions like chronic kidney disease and hypertriglyceridemia ,vitamin B12 deficiency, iron deficiency anaemia can co- exist and some conditions can be the effect of the treatment itself, such as vitamin b12 deficiency secondary to metformin treatment (4).

Obviously if certain conditions affect the accuracy and validity of HBA1C, then is there any alternative biomarker to HBA1C than can be used in most of these medical conditions? This was the second part of our survey and the answer is given in Figure 4.

Figure 4: Shows Answers to Alternate Biomarker to HBA1C as Percentage, 80 percent Incorrect, 20 percent Correct



This clearly shows that the majority of family physicians are not aware of an alternate test or biomarker to HBA1C, that could be used instead of HBA1C in situations or medical conditions that can affect the accuracy of HBA1C itself.

About 80% of physicians' answers to this was Fasting blood sugar or (OGTT), oral glucose tolerance test, which are both incorrect answers, only 20% suggested glycated albumin which is the correct answer.

Discussion

Although HBA1C is a standard test in diagnosis and management of type 2 diabetes mellitus, there are different medical conditions that can affect its levels, especially conditions that can effect survival or longevity of red blood cells.(2) (5)

Different studies have shown that iron deficiency anaemia is associated with falsely increased levels of HBA1C which can result in both misdiagnosis and management of type 2 diabetes mellitus (7). On the contrary taking iron and treating iron deficiency anaemia lowers HBA1C as iron deficiency improves both in pregnant and non-pregnant subjects v(8)(9).

Similarly studies have shown that deficiency of vitamin B12 gives false increase in HBA1C and treatment of b12 deficiency decreases HBA1C levels (10)(11)(12).

Genetic disorders of haemoglobin can effect HBA1C readings depending on which haemoglobinopathy , as genetic disorders of haemoglobin are more common in African and Asian populations, Health care professionals should be vigilant as these genetic disorders of haemoglobin can give falsely high or low values of HBA1C; glycated albumin can instead be used for their glycaemic control (13)(14).

Depending on the stage of chronic kidney disease and shortened survival red blood cell time in advanced renal disease this can affect the accuracy of HBA1C(15).

Also, HBA1C is not a reliable test especially in advanced CKD and haemodialysis, so glycated albumin can be a way forward (16).

Cirrhosis due to resulting anaemia, and sequestration of red blood cells by enlarged spleen, can give falsely high HBA1C (17)(18).

So, if reliability and efficacy of HBA1C is affected in the above conditions, especially chronic kidney disease, some haemoglobinopathies and liver disease, is there an alternate biomarker? The answer is yes.

That is glycated albumin (19).

Figure 5

Box 1 Factors that influence HbA_{1c} and its measurement

- Erythropoiesis
  - Increased HbA_{1c}: iron, vitamin B_{12} deficiency, decreased erythropoiesis.
  - Decreased HbA_{1c}: administration of erythropoietin, iron, vitamin B_{12}, reticulocytosis, chronic liver disease.
- Altered haemoglobin
  - Genetic or chemical alterations in haemoglobin: haemoglobinopathies, methaemoglobin, may increase or decrease HbA_{1c}.
- Glycation
  - Increased HbA_{1c}: alcoholism, chronic renal failure, decreased intraerythrocytic pH.
  - Decreased HbA_{1c}: aspirin, vitamins C and E, certain haemoglobinopathies, increased intraerythrocytic pH.
  - Variable HbA_{1c}: genetic determinants.
- Erythrocyte destruction
  - Increased HbA_{1c} (increased erythrocyte life span): splenectomy.
  - Decreased HbA_{1c} (decreased erythrocyte life span): haemoglobinopathies, splenomegaly, rheumatoid arthritis or drugs such as antiretrovirals, ribavirin and dapsone.
- Assays
  - Increased HbA_{1c}: hyperbilirubinaemia, carbamylated haemoglobin, alcoholism, large doses of aspirin, chronic opiate use.
  - Decreased HbA_{1c}: hypertriglyceridemia.
  - Variable HbA_{1c}: haemoglobinopathies.

Glycated albumin is superior to HBA1C specially with rapid changes in glycaemia or rapid red cell turnover such as in haemolytic anaemias, chronic kidney disease haemodialysis.(21)

Glycated albumin is superior to HBA1C in evaluating glycaemic control in advanced chronic kidney disease (22) (19).

In a study in Japan it was demonstrated that during the end of pregnancy when there is increased demand for iron and this can affect the accuracy of HBA1C as the glycated albumin levels remained unaltered (19).

Interestingly poor control of glycemia or therapeutic inertia or no or little response to medications in type 2 diabetes mellitus can be a result of overlooking other factors or medical conditions that can affect the HBA1C (23).

This poor control of HBA1C will not only lead to more complications in patients but also will cause economic burden on the health care system in a country (23).

Electronic research of “Pubmed” database in USA from 2011 TO 2015 suggested that

“there are physician led barriers to achieve good glycaemic control “ and one of them is “the lack of diabetes focussed education as a contributing factor to achieve therapeutic targets” (24).

A survey of 209 primary care physicians in Australia in 2017 concluded that “Nearly half of the primary care physicians reported learning needs related to pharmacological management of T2DM. Many lacked confidence in providing effective insulin treatment.”(24).

Figure 6: Shows the values of glycated albumin in diagnosis of type 2 diabetes mellitus (20). An Alternative Test to Guide the Diagnosis of Diabetes Mellitus

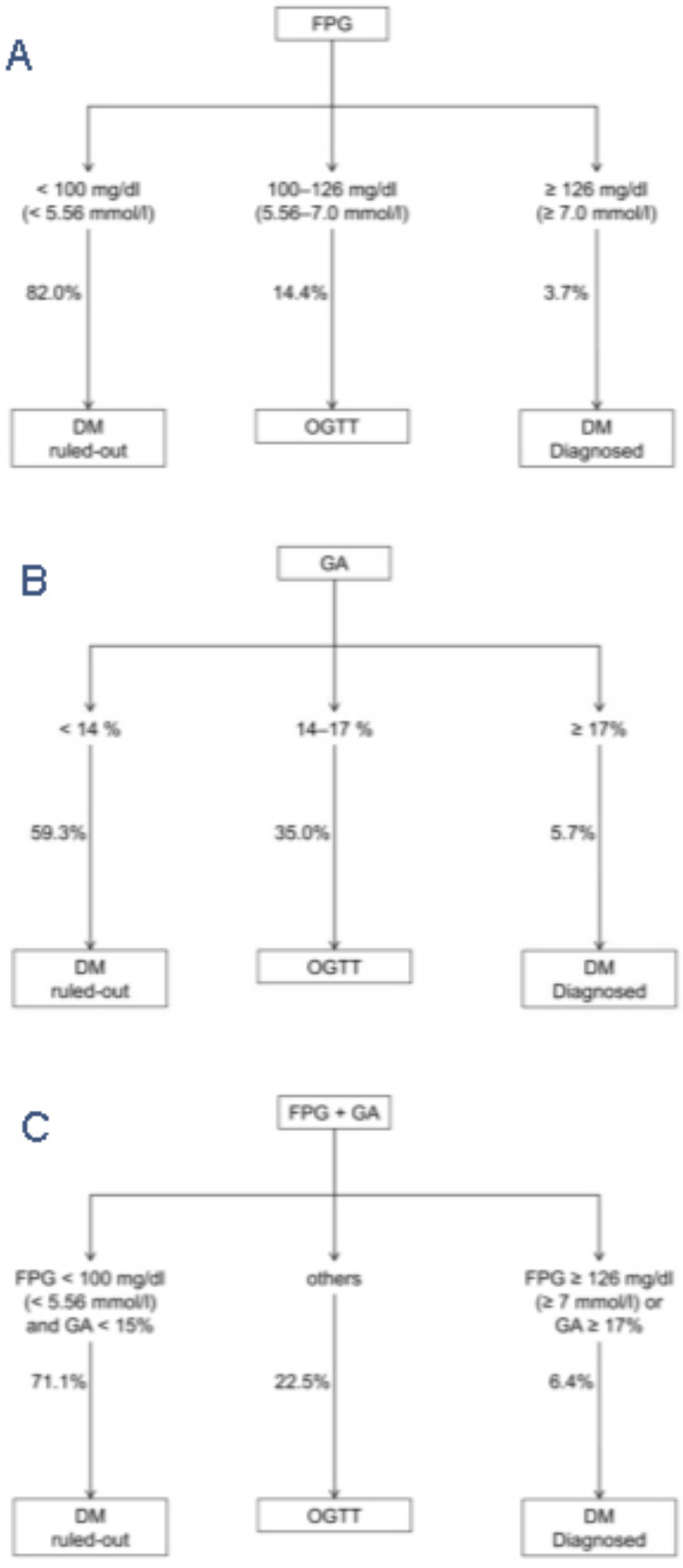


Figure 6: Screening strategies to find diabetes by OGTT.

Proportions of population in specific diagnostic category were shown:

(A) By impaired fasting glucose (IFG) criteria, that is, fasting plasma glucose (FPG) <100 mg/dl 5.56 mmol/L to exclude and FPG ≥ 126mg/dL (7.0 mmol/L) to diagnose diabetes.
The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), false positive rate, (FPR) and false negative rate (FNR) for this strategy were 78.8%, 100%, 100%, 98.1%, 0% and 21.2%

Conclusion

Not achieving therapeutic targets with HBA1C and poor glycaemic control is unfortunately a reality in today's health care in spite of many therapeutic interventions to treat and control type 2 diabetes mellitus.

The reason behind this is multifactorial, but one reason that we have tried to explore in this paper is that primary care physicians need to be more aware and vigilant, in interpreting values of HBA1C. It is not only a number in context to chronic glycemia , this number is affected in its accuracy by many other common medical conditions the majority of which co-exist in patients with diabetes mellitus and some are developed as complications of the disease itself.

Furthermore, it is important in todays advanced healthcare system to be aware of alternative biomarkers that are available instead of HBA1C in a small but definite group of patients, where HBA1C values cannot be depended upon.

This also suggests that more focused training is required in primary care physicians in regard to type 2 diabetes mellitus to prevent therapeutic inertia and to improve glycaemic control.

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(Editorial continued from page 3)

Wani, & Zaidi conducted a study in Jammu And Kashmir examined the prevalence of posttraumatic stress disorder (PTSD) symptoms, depression, and coping mechanisms among the adult civilian population in Indian Kashmir. The Everstine Trauma Response Index-Adapted, the Beck Depression Inventory, and the Coping Resources Inventory were used to assess the three domains. Independent-sample t tests were used between the directly and indirectly traumatized groups to explore each of the five hypotheses of this study. The results showed significant differences for all of the hypotheses. The implications of the study are discussed and recommendations given to address the mental health situation of the victims.

Helvaci et al., reports the most desired values of high density lipoproteins in the metabolic syndromee tried to understand the most desired values of high density lipoproteins (HDL). Patients with plasma HDL values lower than 40 mg/dL were collected into the first, lower than 46 mg/dL into the second, lower than 50 mg/dL into the third, and 50 mg/dL and higher into the fourth groups, respectively. The authors concluded that the highest mean age, female ratio, BMI, FPG, WCH, HT, and DM parallel to the highest HDL and LDL, and the highest CHD in contrast to the lowest HDL and LDL values may show initially positive but eventually negative acute phase proteins functions of HDL and LDL. Due to the lowest mean age, female ratio, BMI, FPG, WCH, DM, and CHD, the most desired values of HDL may be between 40 and 46 mg/dL in the plasma.

Sheykhi, M.T., investigates the quality and quantity of divorce event taking place all over the world more than any time before. While divorce is an stigma in one society, it is a regular norm in the other. Divorce is being facilitated all over the world due to modernization and industrialization in process, and the outcome of social change. Sociologists must be quite vigilant to the phenomenon which is breaking families and creating social problems of all sorts. However, it is the sociology that can judge and assess the demerits of divorce. Many of the apparent social issues emerging such as drug abuse, child labor, criminal behaviors and many more, are somehow or the other associated with divorce. Method of research used in the present article is of qualitative type, and the article eventually concludes that the outcome of divorce is widely different in sociological terms affecting both parties of parents as well as children to a greater extent.

The second part of the review on Parkinson's disease discussed the etiology and pathophysiology of the disease. Parkinson's disease is a common neurodegenerative disorder which involves the loss of nigral dopaminergic neurons in particular. The cause is uncertain but there is growing evidence that this could be due to a combination of ecological and hereditary factors.

Prevalence of Type 2 Diabetes in a Rural Population of AbuNakhla, Doha, Qatar

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Abstract

Objective: Type 2 diabetes (T2DM) is a common condition worldwide and is a rapidly growing epidemic. T2DM prevalence is more common in middle and low-income countries. Once known as a disease of middle and old age, it now more commonly affects the younger population given various risk factors like unhealthy lifestyle, poor health literacy, obesity, and male gender. This study aims at looking at the prevalence of T2DM in a small rural population of AbuNakhla, Doha, Qatar with age and gender distribution.

Method: A cross sectional study was conducted, gathering a total number of patients registered with T2DM at AbuNakhla health center, Doha, Qatar. Patient data was collected from Cerner (database software) in January 2020, categorising them into four age groups; 18 to 35 years, 36 to 50 years, 51 to 65 years and 66 years and above. Also, data was categorised into male and female genders for each age group to find out the proportion of male and female patients in each of the four age groups.

Results: The results showed high disease burden in the local population of AbuNakhla. Around 51% of patients with T2DM are under the age of 50 years, out of which 10% are under the age of 35 years. Also, the number of females with T2DM is quite high under the age of 35 years. Around 49% of patients are above the age of 50 years.

Conclusion: The data showed a high diabetes prevalence in AbunAkhla, Doha Qatar. Prevalence is higher in the younger age group i.e under 50 years with a rapid rise in prevalence in age group 36 to 50 years for both males and females. More community based educational programs are required to increase health literacy and awareness especially for the younger population. This should be aimed at both prevention as well as proper disease management.

Key words: Type 2 Diabetes Prevalence, AbuNakhla, Qatar, PHCC

Introduction

Type 2 diabetes mellitus (T2DM) is a rapidly growing epidemic worldwide. In America more than 30 million people have diabetes i.e 1 in every 10 people has diabetes and around 90% to 95% of these are T2DM. Usually T2DM develops after the age of 45 years but now it is more commonly affecting children, teens and young adults (1) .

In the United Kingdom (UK) around 4.7 million people have diabetes out of which 90% have T2DM, around 8% are type 1 diabetes mellitus (T1DM) and remaining types under 2% (Figure 1). One million people with T2DM are still undiagnosed in UK. In 1996 there were 1.4 million people diagnosed with diabetes and in 2019 3.8 million were diagnosed (2).

As per the International Diabetes Federation (IDF) there are approximately 643 million people (aged 20 to 79 years) living with diabetes worldwide. By 2045 this figure will go up to 700 million. The proportion of people with T2DM is growing worldwide. Around 232 million (1 in 2) people are undiagnosed with diabetes and 374 million are at increased risk of developing T2DM(3).

IDF Middle East and North Africa (MENA) region represents 21 countries with 29 diabetes organisations. Qatar is one of the 21 countries of MENA region. The total adult population of Qatar in 2017 was around 1,844,000 out of which there were 259,200 cases of diabetes , having a prevalence of 14.1% in 2017 (4). According to the World Health Organisation (WHO) diabetes country profile the prevalence of T2DM in the Qatari adult population was around 17%. The high disease prevalence among the adult population is due to the increased labour demand causing a large influx of immigrants in the last decade and by 2020 diabetes alone was estimated to be responsible of 10% mortality in Qatar (5).

In Qatar, the number of people with diabetes aged 20 to 79 years in 2010 was 85 per 1000. This number has increased from 85 to 347 per 1000 in 2019 and this number will increase to 702 per 1000 by year 2045. There are still 125.2 undiagnosed people per 1000 in addition to the above figures (6) (Figure 2).

A prospective cohort study performed by Alyafei et al (2018) looked at the incidence of T1DM and T2DM among aged 0-14 years children in Qatar between 2012 to 2016. A total 440 youths with T1DM and 45 with T2DM were identified for the study. The incidence rate of T2DM increased from 1.82 per 100,000 in 2012 to 2.72 per 100,000 in 2016 with an annual increased incidence of 3.12% (Figure 3)(7).

Similar to the statistics worldwide, of all the diabetes mellitus (DM) cases in Qatar, 90% are of T2DM only. Hereditary and life style risk factors are the main contributors towards development of T2DM (8). To understand the prevalence and risk factors of DM in Qatar, a case-control study was conducted over 459 adult patients with diabetes and 342 control patients over a period of 2 years i.e 2006 to 2008. The results showed being a Qatari national was the strongest risk factor for development of DM. Other risk factors included higher monthly income (≥ 3000 QAR), age > 65 years, male gender, obesity (BMI≥30), no college education and lack of physical activity. This study suggested that eliminating obesity and improving the level of education may reduce the risk of DM cases up to half for Qatari nationals (46.9% and 49.3% respectively) and by one third for the population at large (31.7% and 26.8% respectively) (9).

Figure 1: Taken from Diabetes.org.uk/facts & Figures - Infographics of different types of Diabetes (2)

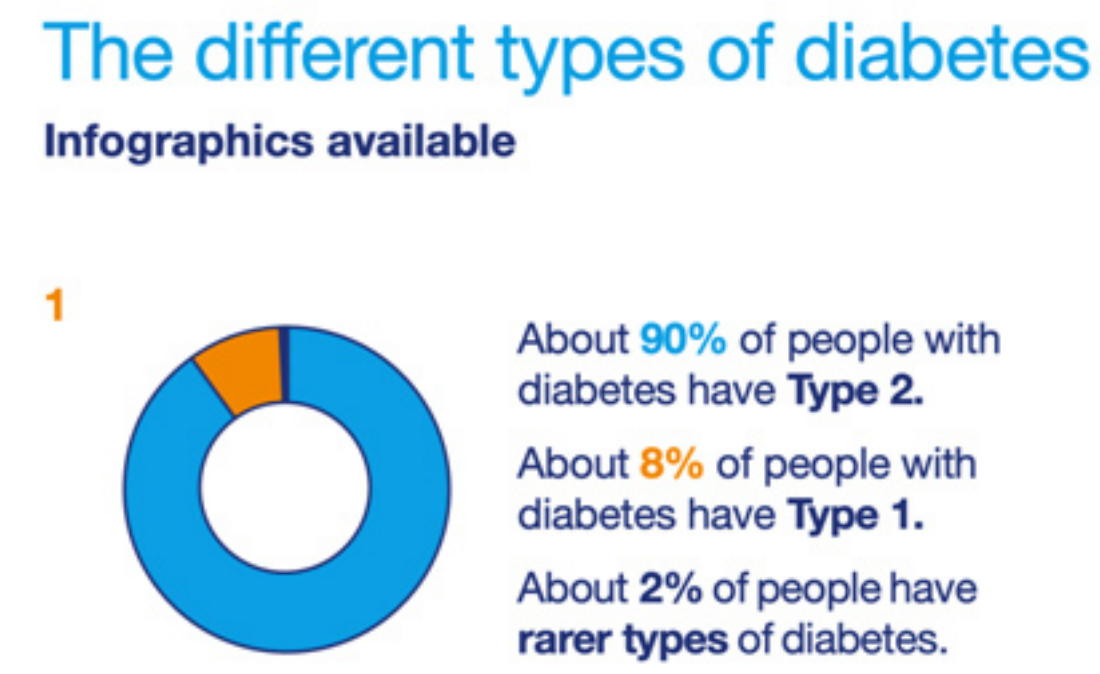


Figure 2: Taken from IDF Diabetes Atlas showing Qatar Country Report 2010 - 2045 (6)

At a glance	2010	2019	2030	2045
Diabetes estimates (20-79 y)				
People with diabetes in 1000s	85.0	347.0	508.7	702.1
Age adjusted comparative prevalence of diabetes %	15.4	15.6	17.0	17.7
People with undiagnosed diabetes in 1,000s	-	125.2	-	-
Proportion of people with undiagnosed diabetes, %	-	36.1	-	-

Figure 3: Taken from Alyafei et al (2018) showing incidence rates of T1DM and T2DM in Qatar from 2012 to 2016

Incidence rates/100,000 for T1DM and T2DM in children and adolescents in Qatar

Year	T1DM	T2DM	Total
2012	25.91	1.82	27.74
2013	26.05	4.40	30.45
2014	24.65	3.48	28.12
2015	33.49	2.07	35.57
2016	31.83	2.72	34.55

According to Weill Cornell Medicine-Qatar (WCM-Q), obesity accounts for 66 % followed by other factors (e.g. genetic) as the leading cause of T2DM in Qatar (Figure 4) and the fraction of Qataris with T2DM is predicted to grow by 147% by year 2050 and T2DM will consume around one third of health expenditure in Qatar by year 2050 (10)(11).

Qatar Diabetes Association (QDA) is a member of IDF and is working on diabetes prevention as well as treatment locally as well as in the region. QDA is providing a free service and has introduced a few educational programs aiming to increase awareness of local population which include educational and social learning camps for children and adults (Al Bawasil Camp & Youth at Risk Camp), diabetes in Asia study group holding biannual conferences and school health visits and awareness drives (12)(13).

Also, the Primary Health Care Corporation (PHCC) in Qatar has already established “SMART Clinics” which play a vital role in screening the adult Qatari population i.e ≥ 18 years for diabetes through glycosylated haemoglobin (HbA1c) levels and categorised them into normal, pre-diabetic or diabetic range as per American Diabetes Association (ADA) guidelines (5)(14).

AbuNakhla is a small district, located in the western region of Qatar and has a primary health care facility known as AbuNakhla Health Center in Mebaireek area, working under the Primary Health Care Corporation (PHCC). PHCC started to work initially in 1954 by providing its services to the local community through a number of clinics. In 1978, the Ministry of Public Health (MoPH) launched the primary health care system through nine health centers all cross Qatar. Now in 2020, the primary health care system has massively grown to 27 health centers providing high quality care across the country.

AbuNakhla health center is one of the 27 health centers built across the country and has around 50,000 registered patients covering AbuNakhla and surrounding areas. (Figure 5)

Figure - 4: Taken from WCM-Q study, showing risk factors for T2DM in Qatari Population (10)(11)

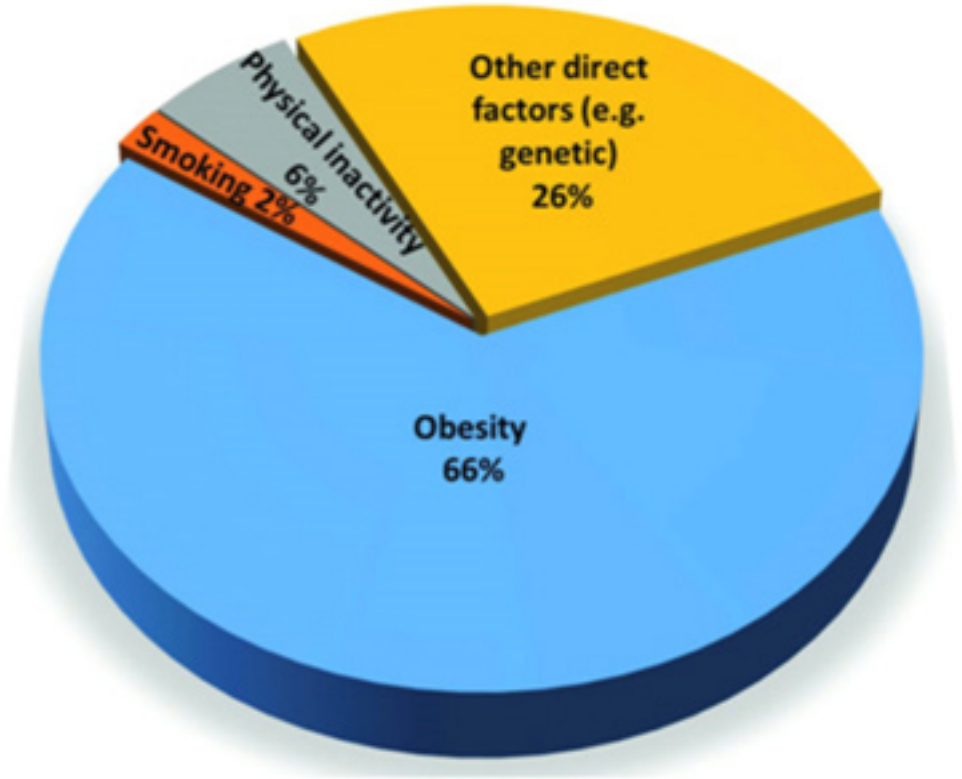


Figure 5: Taken from Google Maps, showing Abu Nakhla location (Pinned area)

As T2DM is usually a disease of middle to old age, this paper focuses on prevalence of T2DM in the rural population of AbuNakhla and gives detailed statistics about T2DM prevalence age wise and gender wise, reflecting which age group has more prevalence of T2DM, either under 50 years or above 50 years of age and also which gender is more affected in each age group. The data will help in arranging the local health and community educational services to target the highest prevalence groups towards prevention as well as proper management of T2DM.

Patients and Methods

Study Design:
A cross-sectional study was conducted at AbuNakhla health center, Doha Qatar. Data was collected from Cerner (computer software) with the help of the IT department. Data collection was done in January 2020 specifically for patients registered under clinical code of "Type 2 Diabetes" from Cerner.

Study Population:
The total registered patient population of AbuNakhla health center is around 50,000 which covers AbuNakhla as well as surrounding areas. The total number of registered T2DM patients (Prevalence) was obtained and was subcategorised under gender (male and female) and 4 different age groups i.e 18 – 35 years, 36 to 50 years, 51 to 65 years and 66 years and above, so an exact prevalence can be obtained for different age groups, both male and female.

Ethical Considerations:
Written approvals from health center manager and IT department were obtained as per local policy.

Results

Out of a total 50,000 registered patients at AbuNakhla health center, the total number of patients coded under T2DM was 1,853. This number included all patients from age 18 years and above.

The total number of patients in group-1 (age group 18 to 35 years) was 197, having a prevalence of 10.63%. In group-2 (age group 36 to 50 years) there were 752 patients, having a prevalence of 40.58%. In group-3 (age group 51 to 65 years) the total number was 645, having a prevalence of 34.80% and in group-4 (age group 66 and above) the total number was 259, having a prevalence 13.97% (Figure 6).

Among all 4 age groups, the highest prevalence of T2DM was between age group 36 to 50 years (40.58%) and the second highest prevalence in age group 51 to 65 years (34.80%). (Figure 7).

For gender distribution, the data showed a higher number of female patients with type 2 diabetes in the younger age group i.e 18 to 35 years initially, but then higher male patients in age range of 36 to 65 years (Figure 8).

The statistics overall showed a high percentage of T2DM in younger age groups, with a 10.63% prevalence in the young age group and 40.58 % prevalence in the middle age group. This means that out of a total 1,853 patients registered under T2DM code, around 51% patients (n=949) are under the age of 50 years only and the rest 49% are above 50 years age group. Among these the affected male population is 57.20% (n=-543) and female population is 42.78% (n=406).

Discussion

This short study clearly describes a higher disease burden in the local rural population of AbuNakhla, Doha, Qatar, affecting younger and middle age population more commonly then elderly i.e. the majority of patients (51%) are under the age of 50 years. Although, this may not be an exact reflection of disease burden in the local community and the actual numbers could be much higher than this as data was collected for patients registered under the code of "Type 2 Diabetes". This excluded the patients coded under "Type 1 diabetes" and also coded wrongly as only "Diabetes Mellitus" or "Hyperglycemia" and would be the limiting factor, but at same time it highlights that the actual numbers and disease burden could be much higher than what is shown and discussed here. More community-based educational and information programs are required to increase health literacy and awareness of the local population in terms of high disease burden, its prevention and management. People need more awareness of different modifiable risk factors like obesity, life style, education by increasing health literacy and understanding to decrease risk factors which lead to development of T2DM at early age groups.

The adaptation of "SMART Clinic" model by PHCC is a huge step towards working in early screening and management of diabetes in the local community. The SMART clinic model offers an early screening among Qatari adult population i.e. age ≥ 18 years, using a multidisciplinary team approach which involves physicians, dieticians, nurses and other health care workers, helping to detect and guide people at risk. Hence, further enhancement of diabetes prevention educational programs in local community can be an option to address the issue. Increasing health literacy and addressing the modifiable risk factors at an earlier age are likely going to help in lowering the disease burden in the local population.

In order to provide more information and education to the local population, there is a need to reach more members of the community, because providing education within the community helps the educator to reach a large number of the population. Also, community-based programs should be designed to maximise the effects and impact of education and efforts of diabetes prevention and education. These community based educational programs can be delivered through different settings including school health and education programs, work site awareness programs, local community center information programs, through local health center and health care providers, through shopping

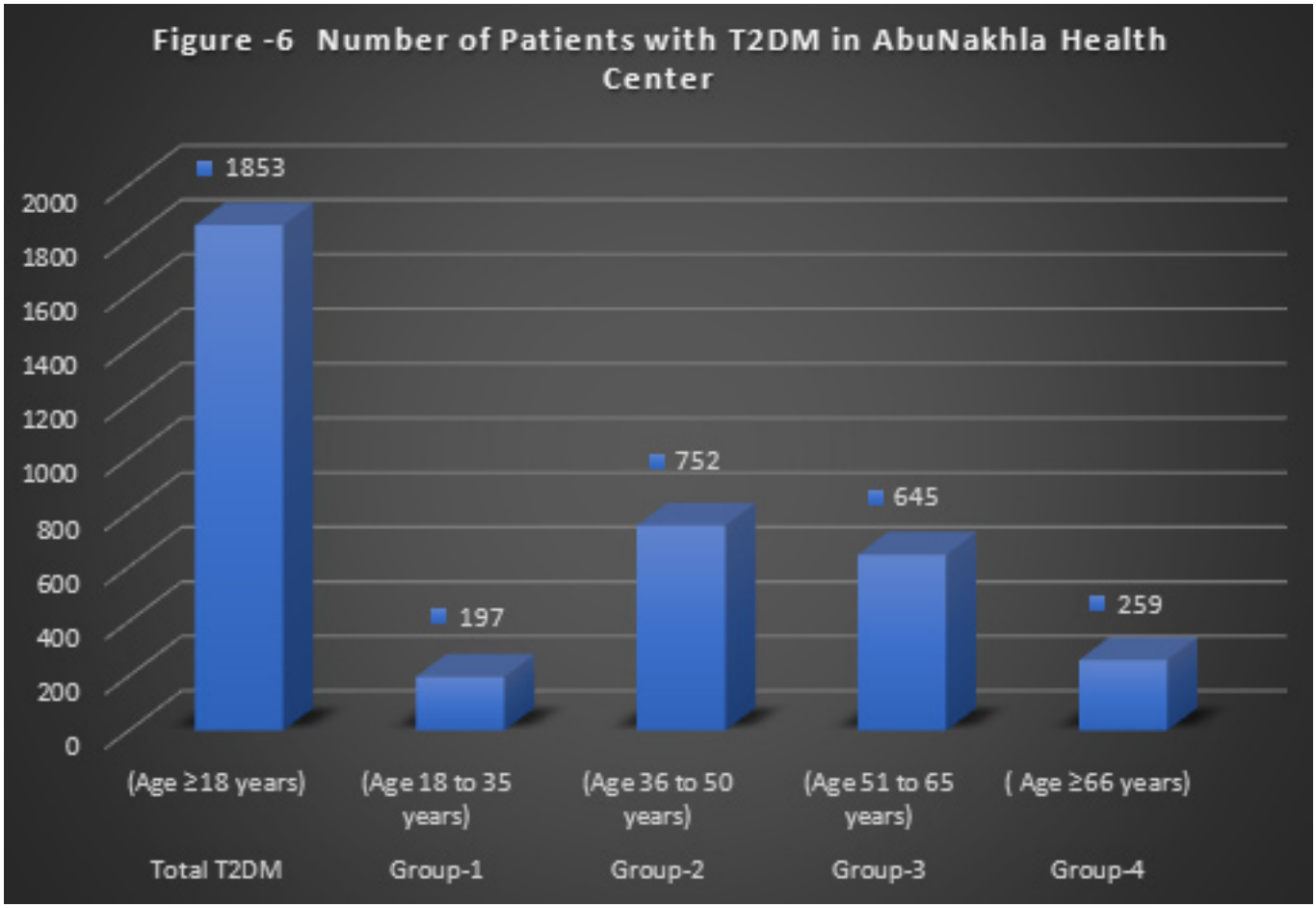


Figure -6 Number of Patients with T2DM in AbuNakhla Health Center
1853
197
752
645
259
2000
1800
1600
1400
1200
1000
800
600
400
200
0
(Age ≥18 years)
(Age 18 to 35 years)
(Age 36 to 50 years)
(Age 51 to 65 years)
(Age ≥66 years)
Total T2DM
Group-1
Group-2
Group-3
Group-4

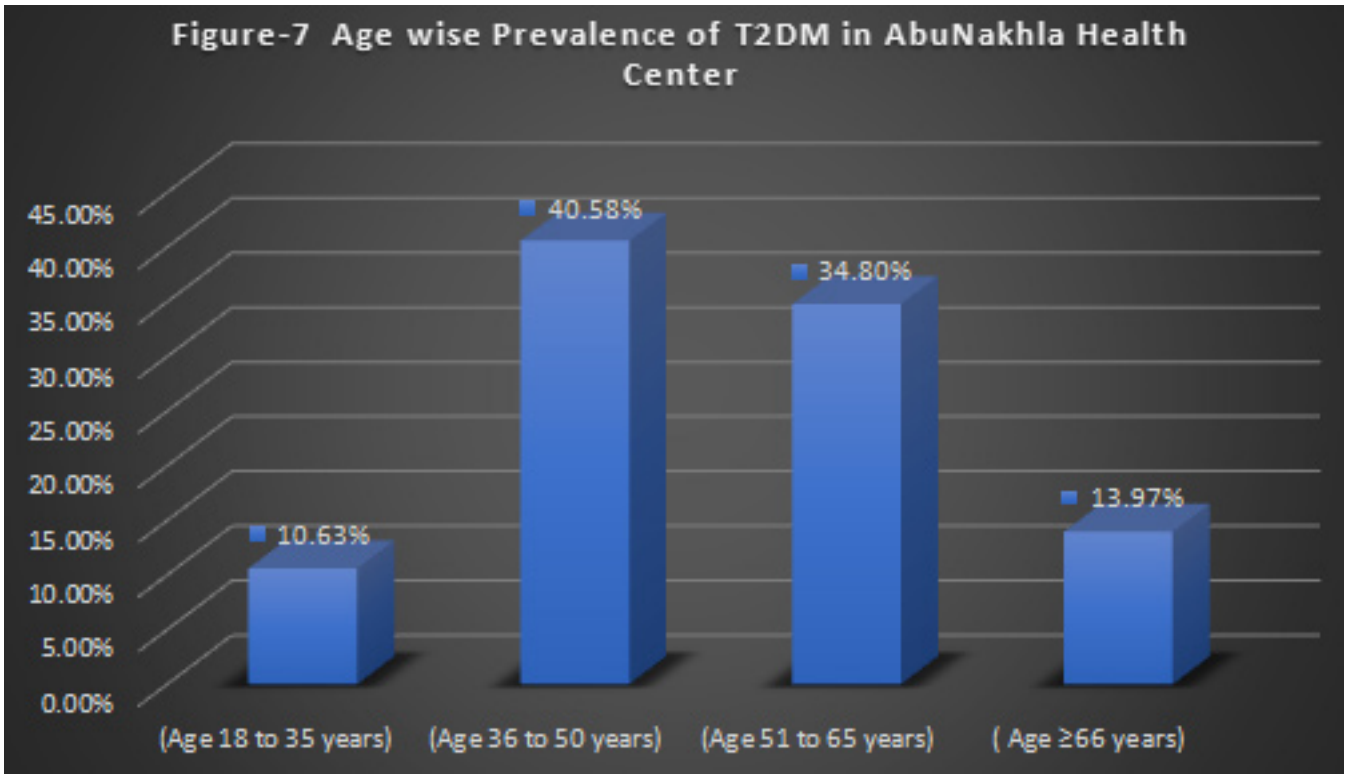
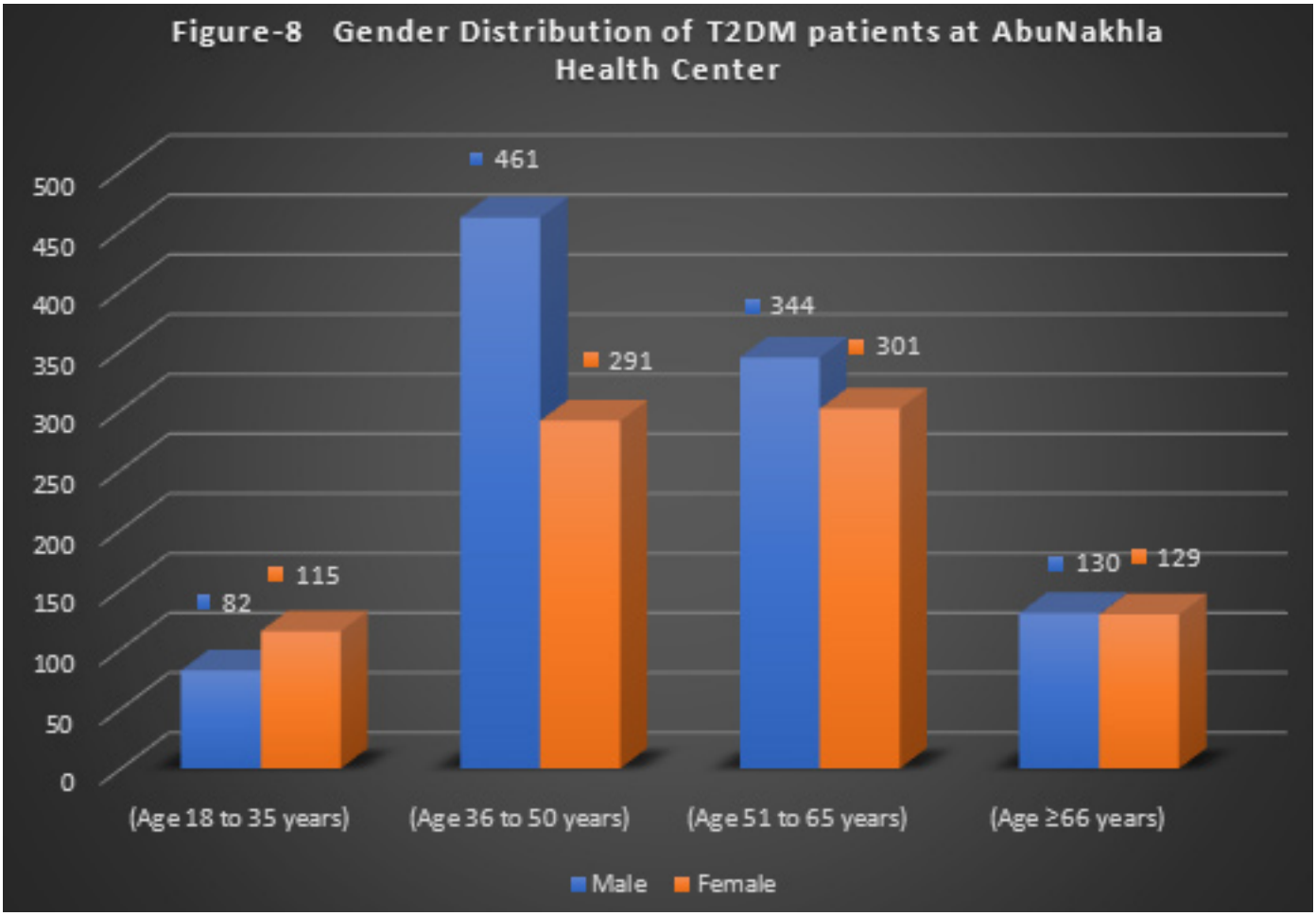


Figure-7 Age wise Prevalence of T2DM in AbuNakhla Health Center
45.00%
40.00%
35.00%
30.00%
25.00%
20.00%
15.00%
10.00%
5.00%
0.00%
10.63%
40.58%
34.80%
13.97%
(Age 18 to 35 years)
(Age 36 to 50 years)
(Age 51 to 65 years)
(Age ≥66 years)



malls and also through local mosques. Utilising these different settings to reach the local population by using existing social and health care resources will definitely help in raising awareness of disease burden and risk in the local community. The aim is to reduce the rate of incidence of developing diabetes and improve the control of existing disease.

Acknowledgments:
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Get Acquainted with the Secret "It's Duration and not the Type of Contact that matters in COVID-19"

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Abstract

Objectives: To quantitatively analyze the impact of type of contact and duraton of contact with infectivity of novel Corona virus.

Material and methods: We analyzed 378 suspects/ cases to prove our null hypothesis. Relevant information was recorded on a predesigned proforma prepared in accordance with the objective of the study, in SPSS version 25th.

Results: Out of 378 suspects, 180(47.61%) were advised PCR based on their higher score on the approved scale. Of the total tested cases, 41/180(22.77%) were COVID-19 positive. History of contact with positive COVID-19 patients was contributing in 35/41(85.36%) confirmed cases. We observed that 25/41(60.97%) of the positive cases had a contact history > 5 days. The relationship of duration of contact with COVID-19 infection was statistically significant (*p=0.001*). 22/41(53.65%) of the positive cases had history of hand shake and hugging, followed by 8/41(19.5%) hand shake only and 5/41(12.19%) with history of mass gathering with a significant relation with viral infectivity (*p=0.02*). A moderate uphill positive correlation of duration of contact was recorded with test positivity (*p=0.001, rho=0.33*) as compared to type of contact (*p=0.14, rho=0.11*). We observed that contact with strong suspect/ COVID-19 patients irrespective of type or duration of contact , the probability and relative risk of acquiring infection was 6 times (*OR=6.1, rr=1.82*) more than in case with no history of contact. When the type of contact was kept as static variable and measured the probability for an increase in duration of contact , the probability and relative risk of COVID increases by 26 times (*OR=26, rr=2.83*) as compared to no contact group. At static duration of contact variable, the probability and relative risk for type of contact for COVID-19 was (*OR=1.4, rr=1.03*) as compared to no contact group.

Conclusion: It is the duration of contact and not the type of contact that has a statistically significant correlation and a higher probability of exposure to COVID-19.

Key words: COVID-19, type of contact, duration of contact , correlation, relationship, risk estimation.

Introduction

In China unprecedented measures were taken well in time to control the rapid spread of COVID-19 epidemics. They succeeded in keeping people in homes that were properly achieved by their improved awareness, attitude and approach towards COVID-19(1). COVID-19 (Corona virus disease) was first reported from the metropolitan city, Wuhan, Hubei province of China in Dec 2019 and caused severe respiratory disease/pneumonia. The etiology of COVID-19 is yet to be confirmed, but the majority of scientists agree that it most likely originated from the zoonotic Corona virus, SARS-CoV that emerged in 2002(2). Corona Virus disease termed as COVID-19, is an emerging highly contagious respiratory disease that is caused by novel Corona virus. Its main clinical symptoms are fever, dry cough, fatigue, and dyspnea(3). Regarding the spread of the disease, the basic reproduction number for COVID-19 is 2.3 as compared to influenza virus with a reproduction number of 1.3. Hence the risk of transmission in case of COVID-19 is 1.8 times more than influenza virus (4).

Studies from the epidemic areas have reported different presentations of COVID suspects/patients. A study from China reported fever (23, 82.1%), dry cough (22, 81%) and dyspnoea (14, 50.0%) and lymphopaenia (23, 82.1%) in their study patients(5). There is limited detail known about the clinical features, presentation and even the incubation period of this deadly virus, which has an impact on the control and surveillance of an infectious disease. The incubation period of the 2019-nCoV is reported from 6 days to 12 days(6). The at risk populations are close contacts of COVID-19 infected patients, healthcare workers, family members of infected patients. A study from the mainland China reported that the infectivity ratio was (89%) in family members and other close contacts of COVID-19 patients(7).

In Pakistan the so for reported data from government sources declares 11,940 confirmed cases with 253 deaths(8). There is a need to know the causes and mechanisms of the spread of the virus in our population. Therefore present study was designed to determine the statistical significance of type and duration of contact with COVID-19 patients and its relation with viral infectivity in our population.

Material and Methods

This cross sectional study was conducted from 5th February to 27th April 2020 in a major tertiary care hospital of Nowshera in collaboration with District Health Office Nowshera. A total of 378 suspected COVID-19 patients were included. Assuming 4% prevalence of COVID-19 in the general population from the study of Zhou X et al (9); a reference population of 100,000 patients was estimated to reside in the catchment area of our hospital, belonging to district Nowshera of Khyber Pakhtunkhwa, Pakistan. A sample size of 378 was calculated through Open-epi software, an online sample size calculator, with Absolute precision of 5%, confidence interval of 95%, and a drop out of 10%.

All the suspects who attended the COVID-19 clinic irrespective of age and gender were randomly selected. All patients with any type of symptoms who came to emergency or outdoor patients department were excluded. Ethical endorsement was obtained from the institutional ethical review board of Nowshera Medical College hospital administration before the execution of the survey. Prior informed consent was obtained from all suspects and they were assured of confidentiality. All those suspects with COVID proforma score more than 5 were subjected for testing their nasopharyngeal swabs for 2019-nCoV. This scoring system applies only on sampling from QHAMC. Data of COVID-19 clinic of Qazi Hussain Ahmed Medical Complex 274 (72.5%), however the patients whose PCR was sent by the district health authorities were also included from the district line list 104 (27.5%). All samples were sent under strict observance of protocols to the Public health research laboratory of Khyber medical university Peshawar (a designated Lab for PCR of 2019nCoV by the Government of Khyber Pukhtunkhwa). All the suspects with score less than five were not subjected to lab investigation, advised precautionary measures and sent home.

Operational definitions

Child: Article 1 of The United Nations Convention on the Rights of the Child defines a child as “for the purposes of the present Convention, a child means every human being below the age of 18 years unless under the law applicable to the child, majority is attained earlier” (10).

Adult: Young adult 19-35 years, middle-aged adult 36-55 years and older adult > 56 years(11).

Data was entered in SPSS 25th version and descriptive and correlation statistics were applied. The frequency and proportion of numerical and categorical variables were presented in percentages. Correlation tests using Spearman ranked correlation was used to determine the correlation of PCR positivity with type and duration of the contacts. Chi-square test was used to show a relationship of the viral infectivity with age categories, type of contact, duration of contact s of the suspects/cases. Relative risk analysis was done for risk estimation in groups with and without history of contact in general, and for the individual variables (type and duration of contact) with strong suspects/COVID-19 patients. Odd ratio was calculated to show the probability of COVID-19 in patients with and without history of contact, type of contact and duration of contact .

The criteria and scoring for patient selection for PCR testing mentioned in Table 1 was approved by the administration of QHAMC on the recommendation of the infectious disease control committee, keeping in view the shortage of Viral Transport Media (VTM) supplied by the government.

Results

Out of 378 suspects, 180(47.61%) were advised PCR based on their higher score on the approved scale. Of the total tested cases 41/180(22.77%) were COVID-19 positive. History of contact with positive COVID-19 patients was contributing in 35/41 (85.36%) confirmed cases. We observed that 25/40 (60.97%) of the positive cases had a contact history > 5 days. The difference in the duration of contact and its relation with COVID-19 infection in term of positivity of test by PCR was highly statistically significant using Chi-Square test (*p=0.001*). (Table 2).

We noted that 22/41 (53.65%) of the positive cases had history of hand shake and hugging, followed by 8/41(19.5%) with history of simple hand shake and 5/41 (12.19%) with history of mass gathering. The difference in the type of contact and its relation with COVID-19 infection in terms of positivity of test by PCR was statistically significant using Chi-Square test (*p=0.02*). (Table 3).

Using Spearman correlation test to quantify the strength of correlation of type and duration of contact with infectivity (test positivity) we observed a moderate uphill positive correlation of duration of contact with test positivity (*p=0.001, rho=0.33*) as compared to type of contact that was not statistically significant (*p=0.14, rho=0.11*). Hence the relationship (one sided from cause to effect) that was observed in Table 3 is attributed to have occurred by chance as there is no correlation of type of contact with test positivity (double sided-interrelation). Here the lesson learned is that it is the duration of contact that is directly related to infectivity and not the type of contact. (Table 4)

Furthermore using risk analysis to stratify the contribution of type of contact versus duration of contact , we observed that contact with strong suspect/ COVID-19 patient irrespective of type or duration of contact , the probability of acquiring infection is 6 times (*OR=6.1*) more than in the case with history of no contact. Similarly the relative risk for contact is (*rr=1.82*) as compared to no history of contact (0.27), confirms it to be a strong risk factor.

Now when we kept the type of contact as static variable and measured the probability for an increase in duration of contact (from 2 hours to more than 5 days), astonishingly it was observed that probability of COVID increased by 26 times (*OR=26*) with relative risk of (*rr=2.83*) as compared to no history of contact (0.10).

When we kept the duration of contact as the static variable and measured the probability for type of contact (from simple hand shaking to hugging and mass gathering), it was observed that probability of COVID increased by 1.4 times (*OR=1.4*) with relative risk of (*rr=1.03*) as compared to no history of contact (0.7). (Table 5)

This analysis statistically supports that it is the *duration of contact* that matters in COVID-19 infection and not the *type of contact.*

Table 1. Criteria for COVID-19 scoring system.	
Fever, Cough, Sorethroat	1 each
Shortness of breath, Travel history to an epidemic areas	2 each
Contact history with confirmed case/ Close relatives of the COVID-19 patients	6
TOTAL :	13
Strategy to act:	
Score <5 :	Quarantine / stay home
Score:6-8	Do Labs & Inform Focal Person
Score:8-10	Labs : Needs Isolation/admission inform Focal Person

Table 2. Viral infectivity and *duration of contact*									
		Duration of contact							Chi-Square test
		2-5 hours	48 hours	3-5 days	>5 days	Not remembered	No Contact	Total	
PCR Categories	Positive	3	7	5	20	3	3	41	
	Negative	9	35	30	27	9	227	337	
Total		12	42	35	47	12	230	378	*p=0.001*

Table 3. Viral infectivity and *type of contact*

		Type of contact					Total	Chi-Square test
		Hand shake	Hand shake and Hug	Mass gathering	No contact	Healthcare worker		
PCR Categories	Positive	8	22	5	6	0	41	
	Negative	54	16	2	44	23	139	
Total		62	40	7	48	23	180	*p=0.02*

Table 4. Spearman's correlation test to quantify the strength of correlation of type and *duration of contact* with infectivity

			PCR Categories	*Duration of contact*	*Type of contact*
Spearman's Rho	PCR Categories	Correlation Coefficient	1.000	*.327***	.110
		Sig. (2-tailed)	.	*.000*	.142
		N	378	378	180
	Duration of contact	Correlation Coefficient	*.327***	1.000	.634**
		Sig. (2-tailed)	*.000*	.	.000
		N	378	378	180
	Type of contact	Correlation Coefficient	.110	.634**	1.000
		Sig. (2-tailed)	.142	.000	.
		N	180	180	180

**. Correlation is significant at the 0.01 level (2-tailed).

Table 5 5.1. Risk Estimate for COVID-19 with positive contact, irrespective of duration and *type of contact*			
		95% Confidence Interval	
	Value	Lower	Upper
Odds Ratio for PCR Categories (Positive / Negative)	*6.6*	2.70	16.12
For cohort Contact History = Yes	*1.82*	1.53	2.15
For cohort Contact History = No	0.27	0.13	0.58
N of Valid Cases	378		
5.2. Risk Estimate for COVID-19, based on *duration of contact* not biased of *type of contact*			
		95% Confidence Interval	
	Value	Lower	Upper
Odds Ratio for PCRCAT (Positive / Negative)	*26.13*	7.89	86.54
For cohort with *duration of contact* = contact (24-hours to more than 5 days)- keeping the *type of contact* un-biased	*2.83*	2.38	3.38
For cohort with history of contact = No	0.10	0.03	0.32
N of Valid Cases	378		
5.3. Risk Estimate for COVID-19 based on *type of contact* , not biased by *duration of contact*			
		95% Confidence Interval	
	Value	Lower	Upper
Odds Ratio for PCRCAT (Positive / Negative)	*1.38*	0.47	4.08
For cohort with *type of contact* = Yes (from Hand shake to hug and mass gathering)- keeping the duration unbiased	*1.03*	0.93	1.15
For cohort *type of contact* = No	0.74	0.28	1.97
N of Valid Cases	378		

Discussion

Research on population is a process to answer a question, to prove or disprove an assumption or hypothesis for a specified population on a specific issue. Here in the present study our null hypothesis was that rate of infectivity is the same for the variables, type and duration of contacts. We tried to know about what matters more, the type of contact or duration of contact . We recruited 378 suspects where 191 (51.1%) of the suspects had history of contacts with strong suspects/patients. There were 41 (27.7%) cases that were positive out of 148 cases that were selected from the total sampling under a strict criteria due to limited number of Viral transport media.

Scoring in such a situation is the need of time to avoid wastage of resources. In many countries they keep in mind the risk factors in the form of age, gender, travel history, higher markers level like d-dimers>1ug/ml etc are the clues that helps clinicians to identify patients for further trial(12).

We observed that 25/41 (60.97%) of the positive cases had a contact history > 5 days. The relationship of duration of contact with COVID-19 infection was statistically significant (*p=0.001*). Anzai A et al(13) reported a lower rate of infectivity proportion of 30% for history of close contacts while Qiu H et al(7) reported 89% in a study reported from mainland China.

The rate of infectivity depends widely on the incubation period that is reported between 2-14 days in the literature and also on the duration of exposure and also on the immune status of the patient to acquire infection(14).

A study reported in Lancet showed that the attack rate in COVID-19 infection in close contacts of the confirmed cases is 7%, but 80% of the suspects would develop mild symptoms but that would resolve and may not progress into the disease (COVID-19), while a further 3% would need intensive care. The exposure duration matters irrespective of the type of contact s with these cases that supports our findings(15).

A moderate uphill positive correlation of duration of contact with test positivity was (*p=0.001, rho=0.33*) as compared to type of contact (*p=0.14, rho=0.11*). When the type of contact was kept as a static variable and measured the probability for an increasing duration of contact , the probability and relative risk of COVID increases by 26 times (*OR=26, rr=2.83*). Another study from China reported that

there was a moderate uphill positive Spearman correlation of duration of exposure in days with COVID-19 and its complications (*p=0.01, r=0.68*) (16) that coincides with our findings.

Hence stress should be given on duration of exposure to a positive cases as compared to type of contact like shaking hand, hugging or mass gathering. China has succeeded to control and get rid of this deadly virus by taking strict action, including suspension of public transport, closing of recreation places, ban on social gathering and isolation and care of suspected cases in quarantine to succeed in the fight against Corona(1,13,17).

Finally we concluded that it is the duration of contact and not the type of contact that has a statistically significant correlation with COVID-19 infection. This would support the WHO declaration that the dead body can be buried with all religious privileges in a short span of time. Because it is the duration of contact that means and to the lesser extent type of contact.

There are some limitations like delayed diagnosis, stigma associated with disease, lesser exposure to contact patients for their opinion and proper history in this crucial timings, that does not allow us to know the exact time required for transmission of virus from a diseased patient to an asymptomatic person to get infected. This would help the clinicians and public health experts to decide "how much duration" for transmission of infection. This would resolve many issues like burial of the deceased with Corona and to give them proper religious protocol and to please the relatives of the deceased as there is a social stigma associated with this disease and people are afraid to attend the hospitals and they die at home, not tested and this is more dangerous in term of viral transmission behind the stigma.

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The most desired values of high density lipoproteins in the metabolic syndrome

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Abstract

Background: We tried to understand the most desired values of high density lipoproteins (HDL).

Methods: Patients with plasma HDL values lower than 40 mg/dL were collected into the first, lower than 46 mg/dL into the second, lower than 50 mg/dL into the third, and 50 mg/dL and higher into the fourth groups, respectively.

Results: The study included 256 cases (153 females), totally. Parallel to the highest HDL values, the mean age, female ratio, body mass index (BMI), fasting plasma glucose (FPG), low density lipoproteins (LDL), white coat hypertension (WCH), hypertension (HT), and diabetes mellitus (DM) were the highest in the fourth group. Whereas coronary heart disease (CHD) was the highest in the first group in contrast to the lowest HDL and LDL values. Interestingly, the mean age, female ratio, BMI, FPG, WCH, DM, and CHD were the lowest in the second group. Triglycerides were the highest parallel to the highest prevalence of smoking in the second, and they were the lowest parallel to the lowest prevalence of smoking in the fourth groups.

Conclusions: The highest mean age, female ratio, BMI, FPG, WCH, HT, and DM parallel to the highest HDL and LDL, and the highest CHD in contrast to the lowest HDL and LDL values may show initially positive but eventually negative acute phase proteins functions of HDL and LDL. Due to the lowest mean age, female ratio, BMI, FPG, WCH, DM, and CHD, the most desired values of HDL may be between 40 and 46 mg/dL in the plasma.

Key words: High density lipoproteins, low density lipoproteins, triglycerides, acute phase proteins, body mass index, smoking, metabolic syndrome

Introduction

Chronic endothelial damage may be the most common type of vasculitis, and the leading cause of end-organ insufficiencies, aging, and death in the human being (1-4). Much higher blood pressure (BP) of the afferent vasculature may be the major underlying mechanism by inducing recurrent injuries on vascular endothelium. Probably, whole afferent vasculature including capillaries are mainly involved in the process. Thus the term of venosclerosis is not famous in the medical literature. Due to the chronic endothelial damage, inflammation, edema, and fibrosis, vascular walls thicken, their lumens narrow, and they lose their elastic natures, those eventually reduce blood flow to terminal organs and increase systolic BP further. Some of the well-known underlying causes and indicators of the inflammatory process are physical inactivity, sedentary lifestyle, animal-rich diet, smoking, alcohol, overweight, hypertriglyceridemia, dyslipidemia, impaired fasting glucose, impaired glucose tolerance, white coat hypertension (WCH), chronic inflammations and infections, and prolonged cancers for the development of terminal consequences including obesity, hypertension (HT), diabetes mellitus (DM), cirrhosis, peripheric artery disease (PAD), chronic obstructive pulmonary disease (COPD), coronary heart disease (CHD), chronic renal disease (CRD), mesenteric ischemia, osteoporosis, stroke, other end-organ insufficiencies, early aging, and premature death (5-10). Although early withdrawal of the underlying causes can delay terminal consequences, after development of HT, DM, cirrhosis, COPD, CRD, CHD, PAD, mesenteric ischemia, osteoporosis, stroke, other end-organ insufficiencies, and aging, endothelial changes cannot be reversed completely due to their fibrotic nature. The underlying causes and terminal consequences are researched under the titles of metabolic syndrome, aging syndrome, and accelerated endothelial damage syndrome in the literature, extensively (11-13). Although their normal limits have not been determined clearly yet, increased plasma triglycerides values may be one of the most sensitive indicators of the metabolic syndrome (14-17). Due to the growing evidence about the strong association between higher plasma triglycerides and prevalence of CHD, Adult Treatment Panel (ATP) III determined lower cutpoints for triglycerides abnormalities than did ATP II (18, 19). Although ATP II determined the normal plasma triglycerides values as lower than 200 mg/dL in 1994 (19), World Health Organisation in 1999 (20) and ATP III in 2001 reduced the normal limits as lower than 150 mg/dL (18). Although these cutpoints, there are still suspicions about the safest values of plasma triglycerides in the plasma (15-17). Beside that although the higher sensitivity of plasma triglycerides in the metabolic syndrome, basic functions and desired values of high density lipoproteins (HDL) and low density lipoproteins (LDL) are still suspicious (21). We tried to understand the most desired values of HDL in the metabolic syndrome.

Material and Methods

The study was done in the Internal Medicine Polyclinic of the Dumlupinar University between August 2005 and March 2007. Consecutive patients at the age of 15 years and greater were included into the study. Medical pasts of the cases including HT, DM, COPD, and already used medications were learned, and a routine check up including fasting plasma glucose (FPG), HDL, LDL, and triglycerides was performed. Current daily smokers with six pack-months and cases with a past of three pack-years were accepted as smokers. Due to the very low prevalence of alcoholism in Turkey (22), we did not include regular alcohol intake into the study. Patients with devastating illnesses including type 1 DM, malignancies, acute or chronic renal failure, chronic liver diseases, hyper- or hypothyroidism, and heart failure were excluded to avoid their possible effects on body weight. Additionally, anti-hyperlipidemic drugs, metformin, and acarbose users were excluded to avoid their possible effects on blood lipid profiles and body weight (23, 24). Body mass index (BMI) of each case was calculated by the measurements of the Same Physician instead of verbal expressions. Weight in kilograms is divided by height in meters squared (18). Patients with an overnight FPG value of 126 mg/dL and higher on two occasions or already using antidiabetic medications were defined as diabetics (18). An oral glucose tolerance test with 75-gram glucose was performed in cases with a FPG value between 110 and 126 mg/dL, and diagnosis of cases with a 2-hour plasma glucose value of 200 mg/dL and greater is DM (18). Additionally, office blood pressure (OBP) was checked after a 5-minute rest in seated position with a mercury sphygmomanometer on three visits, and no smoking was permitted during the previous 2-hours. A 10-day twice daily measurement of blood pressure at home (HBP) was obtained in all cases, even in the normotensives in the office due to the risk of masked HT after a 10-minute education about proper BP measurement techniques (25). An additional 24-hour ambulatory blood pressure monitoring was not taken due to the similar effectivity with the HBP measurements (3). Eventually, HT is defined as a mean BP of 140/90 mmHg and higher on HBP measurements, and WCH as an OBP of 140/90 mmHg and higher but a mean HBP measurement of lower than 140/90 mmHg (25). An exercise electrocardiogram is performed just in cases with an abnormal electrocardiogram and/or angina pectoris. Coronary angiography is taken just for the exercise electrocardiogram positive cases. So CHD is diagnosed either angiographically or with the Doppler echocardiographic findings as the already developed movement disorders in the cardiac walls. The spirometric pulmonary function tests were performed in required cases after the physical examination, and the criterion for diagnosis of COPD is post-bronchodilator forced expiratory volume in one second/forced vital capacity of less than 70% (26). Finally, patients with plasma HDL values lower than 40 mg/dL were collected into the first, lower than 46 mg/dL into the second, lower than 50 mg/dL into the third, and 50 mg/dL and higher into the fourth groups, respectively. The mean age, female ratio, smoking, BMI,

FPG, triglycerides, LDL, HDL, WCH, HT, DM, COPD, and CHD were detected in each group, and compared in between. Mann-Whitney U test, Independent-Samples T test, and comparison of proportions were used as the methods of statistical analyses.

Results

The study included 256 cases (153 females and 103 males), totally. Parallel to the highest HDL values, the mean age, female ratio, BMI, FPG, LDL, WCH, HT, and DM were the highest in the fourth group. Whereas CHD was the highest in the first group in contrast to the lowest HDL and LDL values. Interestingly, the mean age, female ratio, BMI, FPG, WCH, DM, and CHD were the lowest in the second group. Triglycerides were the highest parallel to the highest prevalence of smoking in the second, and they were the lowest parallel to the lowest prevalence of smoking in the fourth groups. So prevalence of smoking was parallel with the male ratio in the study (Table 1).

Discussion

Adipose tissue produces leptin, tumor necrosis factor-alpha, plasminogen activator inhibitor-1, and adiponectin-like cytokines acting as acute phase reactants in the plasma (27, 28). Excess weight-induced chronic low-grade vascular endothelial inflammation plays a significant role in the pathogenesis of accelerated atherosclerosis in whole body (1, 2). Additionally, excess weight leads to myocardial hypertrophy terminating with a decreased cardiac compliance. Combination of these cardiovascular risk factors eventually terminate with increased risks of arrhythmias, cardiac failure, and sudden cardiac death. Similarly, the prevalence of CHD and stroke increased parallel to the increased BMI in the other studies (29, 30), and risk of death from all causes including cancers increased throughout the range of moderate to severe weight excess in all age groups (31). The relationship between excess weight, elevated BP, and hypertriglyceridemia is described in the metabolic syndrome (14), and clinical manifestations of the syndrome include obesity, dyslipidemia, HT, insulin resistance, and proinflammatory and prothrombotic states (12). For example, prevalence of excess weight, DM, HT, and smoking were all higher in the hypertriglyceridemia group (200 mg/dL and higher) in a previous study (32). On the other hand, the prevalence of hyperbetalipoproteinemia were similar both in the hypertriglyceridemia and control groups in the same study (32). Additionally, although the higher plasma trigycerides values, LDL values were also lower in the group with the plasma HDL levels lower than 40 mg/dL in the other study ($p<0.001$ for all) (33).

Table 1: Characteristics features of the cases according to high density lipoproteins values in the plasma

Variable	Lower than 40 mg/dL	*p*-value	Lower than 46 mg/dL	*p*-value	Lower than 50 mg/dL	*p*-value	50 mg/dL and higher
Number	75		63		45		73
Age (year)	45.4 ± 15.2 (16-79)	Ns*	45.3 ± 15.1 (19-78)	Ns	*46.5 ± 13.5 (19-73)*	*0.026*	*51.8 ± 11.6 (21-77)*
Female ratio	46.6%	Ns	*42.8%*	*0.001>*	*66.6%*	*0.01>*	*83.5%*
Smoking	34.6%	Ns	36.5%		24.4%	Ns	17.8%
BMI† (kg/m^2)	27.2 ± 4.5 (18.4-39.9)	Ns	*25.7 ± 4.2 (18.6-34.3)*	*0.024*	*27.7 ± 4.6 (19.6-36.0)*	Ns	29.3 ± 6.1 (17.8-48.6)
FPG‡ (mg/dL)	*119.4 ± 48.4 (76-287)*	*0.006*	*97.6 ± 13.5 (67-154)*	Ns	114.9 ± 59.0 (63-386)	Ns	134.1 ± 77.0 (74-400)
Triglycerides (mg/dL)	162.7 ± 92.8 (43-470)	Ns	175.3 ± 103.0 (27-617)	Ns	144.9 ± 72.2 (47-411)	Ns	134.5 ± 81.5 (37-418)
LDL§ (mg/dL)	*105.3 ± 33.1 (10-211)*	*0.000*	*126.0 ± 32.7 (39-197)*	Ns	134.7 ± 36.6 (77-223)	Ns	135.3 ± 32.3 (54-239)
HDL‖ (mg/dL)	*34.1 ± 3.8 (22-39)*	*0.000*	*42.8 ± 1.6 (40-45)*	*0.000*	*47.5 ± 1.1 (46-49)*	*0.000*	*58.2 ± 8.0 (50-91)*
WCH**	25.3%	Ns	23.8%	Ns	31.1%	Ns	36.9%
HT***	10.6%	Ns	11.1%	Ns	*17.7%*	*0.05>*	*28.7%*
DM****	*21.3%*	*0.001>*	*3.1%*	*0.001>*	*22.2%*	Ns	23.2%
COPD*****	14.6%	Ns	17.4%	Ns	20.0%	Ns	10.9%
CHD******	*20.0%*	*0.05>*	*11.1%*	Ns	13.3%	Ns	16.4%

*Nonsignificant ($p>0.05$) †Body mass index ‡Fasting plasma glucose §Low density lipoproteins ‖High density lipoproteins **White coat hypertension ***Hypertension ****Diabetes mellitus *****Chronic obstructive pulmonary disease ******Coronary heart disease

Similarly, plasma triglycerides were higher in the first group with the lowest LDL and HDL values in the present study. On the other hand, the lowest triglycerides value of the fourth group can be explained by the lowest prevalence of smoking and male ratio since there is a significant relationship between hypertriglyceridemia, smoking, and male ratio (34, 35).

Probably, alcohol and smoking are also found among the most common causes of vasculitis. Both of them cause a chronic inflammatory process on the vascular endothelium depending on the concentrations of products of alcohol and smoke in the blood. So both of them can cause an accelerated atherosclerosis, end-organ insufficiencies, early aging, and premature death. Thus both of them should be added into the major components of the metabolic syndrome. Atherosclerotic effects of smoking are the most obvious in Buerger's disease. It is an obliterative vasculitis characterized by inflammatory changes in the small and medium-sized arteries and veins, and it has never been reported in the absence of smoking in the literature. On the other hand, smoking in the human being and nicotine administration in animals may be associated with decreased BMI values (36). Nicotine supplied by patch after smoking cessation decreased caloric intake in a dose-related manner (37). According to an animal study, nicotine lengthens intermeal time and decreases amount of meal eaten (38). Additionally, the mean BMI seems to be the highest in the former, the lowest in the current, and medium in never smokers (39). Smoking may be associated with a post cessation weight gain (40). Similarly, although CHD was detected with similar prevalence in both genders, prevalence of smoking and COPD were higher in males against the higher BMI, LDL, triglycerides, WCH, HT, and DM in females (41). Similarly, the incidence of a myocardial infarction is increased six-fold in women and three-fold in men who smoke 20 cigarettes per day (42). In another definition, smoking may be more dangerous for women due to the associated weight excess and its consequences. So smoking is probably a powerful atherosclerotic risk factor with some suppressor effects on appetite (43). Smoking-induced weight loss may be related to the smoking-induced chronic vascular endothelial inflammation all over the body since loss of appetite is one of the major symptoms of the disseminated inflammation in the body. Physicians can even understand healing of the patients by means of normalizing appetite. Several toxic substances found in cigarette smoke get into the circulation by means of the respiratory tract, and cause a vascular endothelial inflammation until clearance from the circulation. But due to the repeated smoking habit, the clearance never terminates. So the patients become ill with loss of appetite, permanently. In another explanation, smoking-induced weight loss is an indicator of being ill instead of being healthy (37-39). After smoking cessation, normal appetite comes back with a prominent weight gain but the returned weight is the patients' physiological weight, actually.

Although ATP III reduced the normal limits of plasma triglycerides as lower than 150 mg/dL in 2001 (18), much lower values may indicate better health conditions (15-17). For example, the greatest number of clinical and laboratory deterioration was observed just above the plasma triglycerides value of 60 mg/dL in the above study (17). Similar to the present study, prevalence of smoking was the highest with the highest triglycerides values in the other study (16) which may also indicate the inflammatory role of smoking in the metabolic syndrome, since triglycerides may actually be sensitive acute phase reactants in the plasma. In the above study (16), the mean age, male ratio, smoking, BMI, FPG, WCH, HT, DM, and COPD increased parallel to the increased plasma triglycerides values from the first up to the fifth groups, gradually. On the other hand, increased plasma triglycerides values by aging may be secondary to the aging-induced decreased physical and mental stresses, whicheventually terminate with onset of excess weight and its consequences. Although the borderline high triglycerides values (150-199 mg/dL) are seen together with physical inactivity and overweight, the high (200-499 mg/dL) and very high triglycerides values (500 mg/dL and greater) may be secondary to smoking, genetic factors, and terminal consequences of the metabolic syndrome such as obesity, DM, HT, COPD, cirrhosis, CRD, PAD, CHD, and stroke (18). But although the underlying causes of the borderline high, high, and very high plasma triglycerides values may be a little bit different, probably risks of the terminal consequences do not change in them. For example, prevalence of HT, DM, and COPD were the highest in the group with the highest triglycerides values in the above study (16). Eventually, although some authors reported that lipid assessment can be simplified as the measurements of total cholesterol and HDL values alone (44), the present study and most others indicated significant relationships between plasma triglycerides, HDL, and LDL values and terminal consequences of the metabolic syndrome (33, 45).

Cholesterol, triglycerides, and phospholipids are the major lipids of the body. Cholesterol is an essential structural component of the animal cell membrane, bile acids, adrenal and gonadal steroid hormones, and vitamin D. Triglycerides are the major lipids of the fat tissue. Phospholipids are triglycerides that are covalently bound to a phosphate group, and regulate membrane permeability, remove cholesterol from the body, provide signal transmission across the membranes, act as detergents, and help in solubilization of cholesterol. Cholesterol, triglycerides, and phospholipids do not circulate freely in the plasma, instead they are bound to proteins, and transported as lipoproteins. There are five major classes of lipoproteins in the plasma. Chylomicrons carry exogenous triglycerides to the liver via the thoracic duct. Very low density lipoproteins (VLDL) are produced in liver, and carry endogenous triglycerides to the peripheral organs. In the capillaries of adipocytes and muscle tissue, VLDL are converted into intermediate density lipoproteins (IDL) by removal of 90% of triglycerides by lipases. Then IDL are degraded into LDL by removal of more triglycerides. So VLDL are the main source of LDL in the plasma, and LDL deliver cholesterol from the liver to the peripheral organs. Although the liver removes the majority of LDL from the circulation, a small amount is uptaken by scavenger receptors of the macrophages which migrate into the arterial walls, and

become the foam cells of atherosclerotic plaques. HDL remove fats and cholesterol from cells including the arterial wall atheroma, and carry the cholesterol back to the liver and steroidogenic organs such as adrenals, ovaries, and testes for excretion, re-utilization, and disposal. All of the carrier lipoproteins are under dynamic control, and are readily affected by diet, illness, drug, and weight excess. Thus lipid analysis should be performed during a steady state. But the metabolic syndrome alone is a low grade inflammatory process on vascular endothelium. Thus the metabolic syndrome alone may be a cause of abnormal lipoproteins levels in the plasma. On the other hand, although HDL are commonly called 'the good cholesterol' due to their roles in removing excess cholesterol from the blood and protecting the arterial wall against atherosclerosis (46), recent studies did not show similar results, and low plasma HDL values may alert us to searching for some inflammatory pathologies in the body (47-49). Normally, HDL show various anti-atherogenic properties including reverse cholesterol transport and anti-oxidative and anti-inflammatory properties (47). However, HDL may become 'dysfunctional' in pathological conditions which means that relative composition of lipids and proteins, as well as the enzymatic activities of HDL are altered (47). For example, properties of HDL are compromised in patients with DM due to the oxidative modification and glycation of HDL, as well as the transformation of HDL proteomes into the proinflammatory proteins. Additionally, three highly effective agents for increasing HDL levels including niacin, fibrates, and cholesteryl ester transfer protein inhibitors did not reduce all cause mortality, CHD mortality, myocardial infarction, and stroke (50). In other words, while higher HDL values may correlate with better cardiovascular health, specifically increasing one's HDL may not increase cardiovascular health (50). So they may just be some indicators instead of the main actors in the metabolic syndrome. Beside that, HDL particles that bear apolipoprotein C3 are associated with increased risk of CHD (51). For example, although the similar mean age, gender distribution, smoking, and BMI in both groups, DM and CHD were higher in the group with the plasma HDL values lower than 40 mg/dL in the above study (33). Similarly, although the lower mean age, BMI, FPG, LDL, and HDL, the highest CHD of the first group may also indicate eventual functions of HDL as the negative acute phase proteins (APP) in the present study.

APP are a group of proteins whose plasma concentrations increase (positive APP) or decrease (negative APP) as a response to inflammation, infection, and tissue damage (52-54). In case of inflammation, infection, and tissue damage, neutrophils and macrophages release cytokines into the blood. The liver responds by producing many positive APP to them. At the same time, productions of some proteins are reduced. Thus these proteins are called negative APP. Some of the well-known negative APP are albumin, transferrin, retinol-binding protein, antithrombin, and transcortin. The decrease of such proteins is also used as an indicator of inflammation. The physiological role of decreased synthesis of such proteins may be protection of amino acids for production of positive APP, effectively. Due to the same reason, production of HDL and LDL may also be suppressed in the liver. In this way, although the similar mean age, gender distribution, smoking, and BMI in both groups, the higher triglycerides, DM, and CHD against the significantly lower HDL and LDL values can be explained in the above study (33). Beside that although the lower mean age, BMI, FPG, LDL, and HDL, the highest CHD of the first group can also be explained by the same theory in the present study. Similarly, although the mean triglycerides, fibrinogen, C-reactive protein, and glucose values were higher in cases with ischemic stroke, the oxidized LDL values did not correlate with age, stroke severity, and outcome in another study (55). Additionally, significant alterations occurred in the lipid metabolism and lipoproteins composition during infections, and triglycerides increased whereas HDL and LDL decreased in another study (56). Furthermore, a 10 mg/dL increase of LDL was associated with a 3% lower risk of hemorrhagic stroke in another study (57). Similarly, the highest HT and DM parallel to the increased LDL and HDL values, and the highest COPD, CHD, and CRD in contrast to the lowest LDL and HDL values may show initially positive but eventually negative acute phase proteins functions of LDL and HDL in the metabolic syndrome in another study (58), and the safest values of LDL were between 80 and 100 mg/dL in the plasma in the same study (58).

As a conclusion, the highest mean age, female ratio, BMI, FPG, WCH, HT, and DM parallel to the highest HDL and LDL, and the highest CHD in contrast to the lowest HDL and LDL values may show initially positive but eventually negative acute phase proteins functions of HDL and LDL. Due to the lowest mean age, female ratio, BMI, FPG, WCH, DM, and CHD, the most desired values of HDL may be between 40 and 46 mg/dL in the plasma.

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Effects of Touch and Massage Care in Advanced Alzheimer Patient: A Pilot Case Report

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Abstract

Objectives: In the advanced stages of Alzheimer disease (AD), communication abilities are lost, and the patient is expressionless, cannot make utterances or move independently, and, in many cases, is bedridden. Though touch and massage have usually been used as one of the occupational therapy intervention methods for various terminally patients, little has been studied about its effect on advanced AD patients.

Methods: The patient was a woman in her late 80s with the most severe level of care need and dementia due to AD. Once a month, over 5 months, unscented jojoba oil was applied to the patient's hands while she was seated on a wheelchair with her hands on a table, and she received 10 minutes of touch and massage care on each hand, for a total of 20 minutes. Salivary amylase activity was measured just before and immediately after every intervention session as a non-invasive indicator which reflects psychological stress.

Results: The average salivary amylase values before and after the 5 times that the patient received the touch and massage care were 185.6 KIU/L (SD = 44.5) and 112.8 KIU/L (SD = 38.3), respectively. A significant decrease was observed (P = 0.043). As for the patient's appearance during the sessions, when she was helped to move her arms onto the tabletop, her arms and legs sometimes stiffened, and she flexed them intermittently, however, the stiffening diminished after the massage began.

Conclusions: Since this was a pilot case study with a single patient, the results cannot be generalized. However, the study showed that touch and massage care could provide pleasant stimulation for an advanced AD patient with verbal communication difficulties and offered the possibility of reducing physical and emotional stress; therefore, it provides important clues for the future occupational therapy intervention and care of advanced AD patients.

Key words: Advanced Alzheimer Disease,
Non-pharmacological intervention,
Occupational Therapy,
Salivary amylase activity,
Touch and massage care

Introduction

Alzheimer disease (AD) is the most common of irreversible progressive neurocognitive conditions, wherein memory and thinking faculties gradually deteriorate. In the advanced stages of the disease, communication abilities are lost, and the patient is expressionless, cannot make utterances or move independently, and, in many cases, is bedridden. As a method of care for advanced AD patients, non-pharmacological interventions have been recommended(1). Various non-pharmacological interventions have been proposed for elderly persons suffering from dementia such as AD, including sensory stimulation interventions such as acupuncture, aromatherapy, touch and massage therapy, and light therapy; cognitive/emotion-oriented interventions such as music therapy, dance therapy, Snoezelen, and reminiscence therapy; and other interventions such as behavior management techniques, therapeutic exercise, and animal-assisted therapy, and positive effects of these interventions on behavioral and psychological symptoms of dementia (BPSD) have been reported(2). Furthermore, most prior studies on touch and massage care have used changes in behavioral and psychological symptoms as outcomes to evaluate the intervention benefits(3). Amano et al. conducted a study with students in their 20s receiving touch and massage care (Tactile Care®), and found a significant improvement in both subjective assessments; Profile of Mode States (POMS), and Relaxation evaluation scale, and objective assessments; Low frequency and high frequency heart rate ratios (LF/HF), and Salivary secreted immunoglobulin A(4). Touch and massage care has been shown to reduce the stress and anxiety of hospitalized patients (5) and to be effective in relieving BPSD (6); similar effects on mental and physical stress reduction are anticipated for elderly persons suffering from dementia.

Most AD patients in previous studies on touch and massage therapy were mild or moderate cases, and most previous studies have relied exclusively on self-report measures (7); thus, there are almost no studies with advanced AD patients for whom communication has become problematic. Since advanced AD patients show little change in facial expression and have difficulties with verbal communication, it is challenging to assess whether a given type of rehabilitation or care is experienced as pleasurable by the patient.

Therefore, this study used an objective indicator, salivary amylase (α-amylase), as an outcome measure to assess the effectiveness of touch and massage care on advanced AD patients. We believe that this could help to increase the possibilities of providing more effective care for patients with communication difficulties.

Case presentation

Case Description

The patient in this case report was a woman in her late 80s who had been diagnosed with AD 9 years previously. The scores of the New Clinical Scale for Rating of Activities of Daily Living of the Elderly (N-ADL), the New Clinical Scale for Rating of Mental States of the Elderly (NM Scale) and the Assessment of Communication and Interaction Skill (ACIS) were 5 (Range: 0-50), 2 (Range: 0-50), and 21 (Range: 20-80), respectively. The patient was at care level 5, the most severe level of care need which is defined by Japanese Ministry of Health, Labour, and Welfare, in the long-term care insurance ranking (8) while her independence degree of daily living for the demented elderly was IV, the most severe level of dementia in the long-term care insurance ranking; she was able to swallow what was placed in her mouth, but required assistance for all other activities. At times, when her body was touched by staff while she was being moved, she would stiffen her muscles and flex her arms and legs intermittently, showing a pained expression on her face. When staff spoke to her, she rarely responded with eye contact; although she occasionally made utterances, communication (understanding and expression) was difficult for her.

The study was conducted according to the principles of the Helsinki Declaration and approved by the Ethics Board of the Department of Control Science for Body and Life Function at the Hiroshima University Graduate School of Biomedical and Health Sciences (approval number: 1505). Given the difficulties in obtaining the patient's consent for the study, the outline and objectives of the study were explained to her husband verbally and in writing, and his written consent was subsequently obtained.

Methods

The salivary amylase activity was measured just before and immediately after the touch and massage care intervention every time. Salivary amylase is secreted both through the direct action of the sympathetic nervous system and through the effects of noradrenaline. Since salivary amylase activity increases with unpleasant stimuli and decreases with pleasant stimuli, it can be used as a measure to determine whether a person experiences a stimulus as pleasant or unpleasant(9). In this study, a special chip was placed under the patient's tongue for 30 seconds to take a salivary sample, and the level of salivary amylase was then measured using a salivary amylase monitor (NIPRO, Osaka, Japan).

Once a month during 5 months, unscented jojoba oil was applied to the patient's hands while she was seated on a wheelchair with her hands on a table, and she received 10 minutes of touch and massage care on each hand, for a total of 20 minutes. The treatment was provided by an experienced occupational therapist who had received training in touch and massage care. The Wilcoxon signed-rank test was used to compare salivary amylase levels

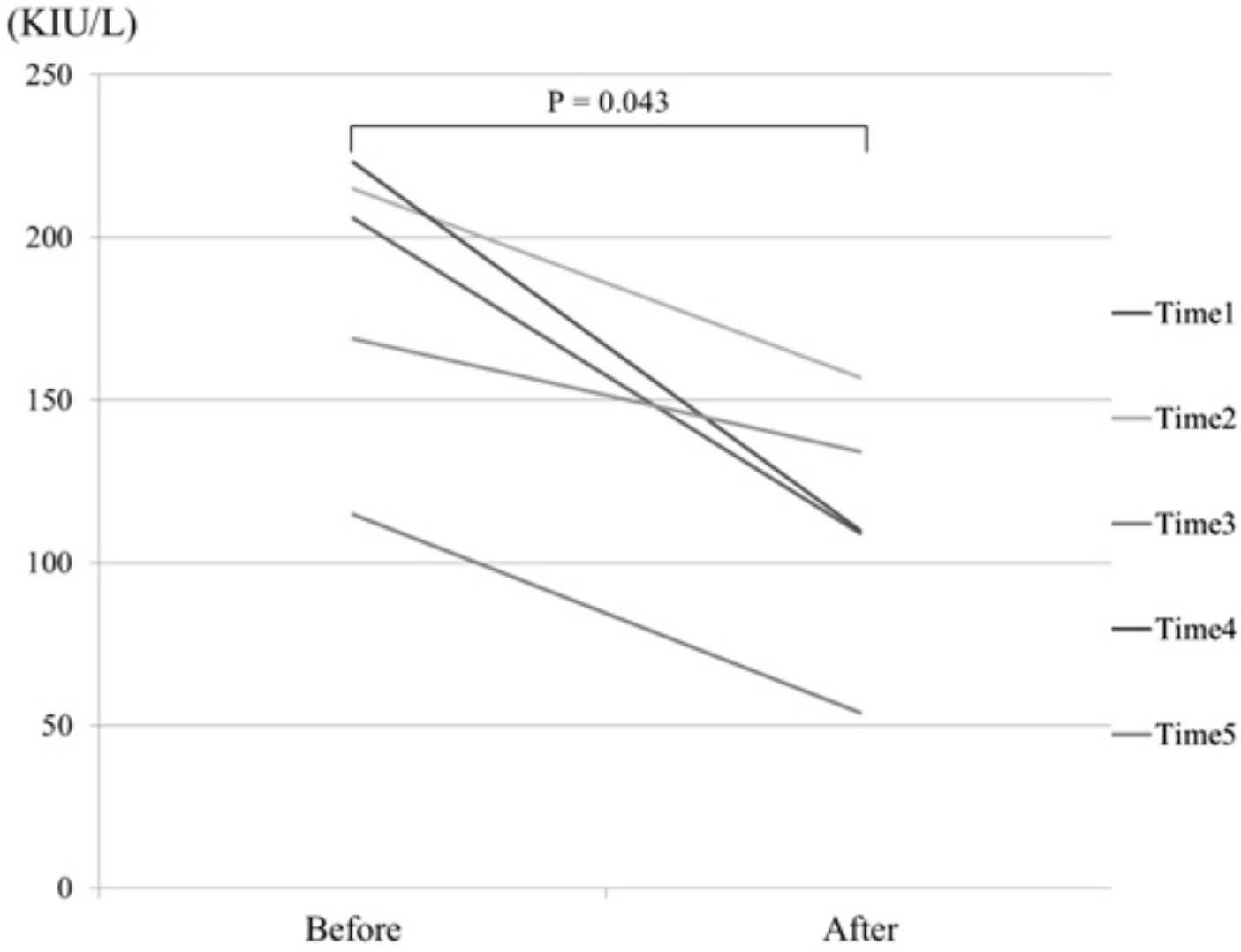
before and after the touch and massage treatment. Statistical analyses were performed using the IBM SPSS 21.0 Statistics (IBM Japan, Tokyo, Japan), with a significance level of 0.05.

Results

Figure 1 shows the change of salivary amylase values between before and after touch and massage care. The average salivary amylase values before and after the 5 times that the patient received the touch and massage treatment were 185.6 KIU/L (SD = 44.5) and 112.8 KIU/L (SD = 38.3), respectively. A significant decrease in salivary amylase activity was observed (P = 0.043).

As for the patient's appearance during the sessions, when she was helped to move her arms onto the tabletop, her arms and legs sometimes stiffened, and she flexed them intermittently, however, the stiffening diminished after the massage began. Additionally, when the OTR asked the patient questions such as "Does it feel good?" she sometimes nodded or responded "Yes, good." When she was given assistance that involved moving her body, she sometimes had a pained facial expression; however, during the massage treatment, she most commonly had a relaxed expression.

Figure 1: The change of salivary amylase values



Discussion

A previous study reported that touch and massage have usually been used as one of the occupational therapy intervention methods for terminally ill patients who have difficulty with active motion or have the need for relaxation or release from pain(10). Although there are some reports that hand massage intervention has beneficial effects to decrease salivary cortisol and alpha amylase as indicator of stress,(11) research on the effectiveness and the use of touch and massage care has not been done sufficiently. In this study, touch and massage care was provided to an advanced AD patient with communication difficulties, and the effects were assessed comparing salivary amylase activity before and after the intervention. Since the level of salivary amylase, which is believed to indicate physical and emotional stress, decreased immediately after the touch and massage treatment, we can infer that the treatment provided to the advanced AD patient in this study had a significant effect in reducing stress. However, in previous studies conducted with older people in long-term care facilities without dementia, we found that while the salivary amylase value decreased immediately after the intervention, 10 minutes after the intervention, the salivary amylase values returned to levels observed before the intervention. Therefore, further research is required to understand how to maintain these effects.

In this particular case, the staff had almost no one-on-one interaction with the patient other than practical care such as help with eating, dressing, and moving, and the question of how they should best interact with the patient was a matter of concern for them. Seeing the patient's changes in facial expression when receiving the touch and massage treatment and observing her interactions with the OTR encouraged the staff to make positive changes in their own interactions with this and other patients.

Since this was a pilot case study with a single patient, the results cannot be generalized. However, the study showed that touch and massage care could provide pleasant stimulation for an advanced AD patient with verbal communication difficulties and offered the possibility of reducing physical and emotional stress; therefore, it provides important clues for the future occupational therapy intervention and care of advanced AD patients. It has also been reported that massage is commonly used by OTRs with terminal-stage cancer patients. Therefore, massage may be effective not only in the rehabilitation of advanced AD patients, but also in palliative care for terminal patients. Therefore, as well as increasing the number of study patients, differences between them should also be considered in future research.

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Do tourists suffer from depression and anxiety disorders?

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Abstract

Objective: To explore the prevalence of depression and anxiety among tourists in Aseer region, KSA.

Method: This is a cross-sectional study conducted during summer 2017 in Abha city, KSA. A quantitative questionnaire was distributed to a sample of 504 participants who attended Summer recreational activities. The questionnaire included demographic data and screening questions for depression (PHQ-9) and Generalized Anxiety Disorder (GAD-7). Data entry and analysis were done using SPSS version 25.

Results: The mean age of the participants was 31±12.5 years; women represented 56%, and 53% were married. More than half of participants (56%) complained of physical symptoms, i.e. chronic headache (14%), chronic joint pain (12%), IBS (10%), and chronic back pain (9%). More than half of participants reported that they visited the PHCC at least once in the past few months.

More than two-thirds had depression (68.9%), (59.5%) have GAD, while both disorders affect (28.4%). Mild depression affects (30.4%), moderate depression (19.8%), while severe depression was reported among (18.7%). Regarding GAD, mild anxiety affected (33.3%), moderate anxiety (17.3%), and severe anxiety was reported among (8.9%). Moderate to severe depression was 38.5%. Women were more affected (44%) than men (31.4%) with a significant difference (p-value = 0.004). Moderate to severe anxiety was more in women (30.3%) compared to men (20.9%) with a significant difference (p-value = 0.018). Age groups did not show significant association with depression or anxiety.

Conclusion and recommendations: This study revealed the high prevalence rates of depression and anxiety among tourists. Most of them complained of physical symptoms, and it could be the cause of frequent health care centres visits. Therefore, depression and anxiety need to be considered in all health care providing levels. Empowering primary mental health care in PHC centres is crucial for providing effective health care for the population.

Key words: Depression, Anxiety, PHQ-9, GAD-7, Tourists, Saudi Arabia

Introduction

Depression and anxiety are two common mental disorders worldwide. More than 300 million people are suffering from depression, as reported by the World Health Organization(1). WHO/Wonca report in (2017) demonstrated that 60% of patients attending the Primary care setting are suffering from depression and or anxiety which is mostly missed (2). In a recent study conducted in an Eastern Province of Saudi Arabia high rates of depression and anxiety reported similar high figures (3). Depression and Generalized Anxiety Disorder(GAD) could coexist in about 30-50% of affected people, and they have common prevention and management strategies (3-4). A recent WHO study estimated that depression and anxiety disorders cost about US$ 1 trillion each year regarding lost productivity (5).

In the Kingdom of Saudi Arabia, a few studies have been conducted to estimate the prevalence of depression and GAD(6-9). Most of these studies reported high rates of prevalence of depression and GAD among the Saudi population. However, these studies targeted either patients attending primary health care settings (3,6-8), or students at colleges (9). This study was conducted during the summer season to estimate the prevalence of depression and GAD among a selected sample of people who attended summer tourist events executed in Abha city, Aseer region, KSA.

Methods

This is a cross-sectional study that was conducted in Aseer region, southwest Saudi Arabia during summer 2017. According to previous studies, the prevalence rate of mental disorder was 60% .

The sample calculation was used as following: margin error=5%, Confidence interval =95%, the total target population = 2,000 individuals. Based on the previous values, the required sample was calculated to be 323.

All individuals 18 years and above, who attended Summer recreational activities, were invited to participate in this study. After obtaining informed consent from the participants, the self-administered questionnaire was distributed and supervised by three of the investigators who explained the purpose of the study and helped participants when needed.

The questionnaire consisted of demographic data, Patient Health Questionnaire-9 (PHQ-9) and Generalized Anxiety

Disorder-7 (GAD-7) as diagnostic screening tools for depression and GAD, respectively. According to PHQ-9, depression was classified into five categories based on the total score as following: none (0-4), mild (5-9), Moderate (10-14), moderate-severe (15-19) and severe (20-27). On the other hand, GAD was classified according to the total score as following: minimal (0-4), mild (5-9), moderate (10-14) and severe (15-21).

Data were entered and analyzed using SPSS version 25. Chi-square test was used to test the association of non-parametric variables with the severity of depression and anxiety. P-values of less than 5% were considered significant.

Official permission to conduct this study was obtained from the concerned authority in General Directorate of Health Affairs, Aseer region. Informed consent was taken from all participants before completing the study questionnaire.

Results

The total participants who completed the questionnaire were 504 individuals. Table 1 shows the participants' characteristics. The mean age (mean ±SD) was 31±12.5 years, women represented 56%, and 96% were Saudi. More than half (53%) of participants were married while 96% were educated.

Table 2 depicts the current complaints among participants. More than one third (44%) had no complaints. Thus, most of the participants had complaints of physical symptoms 283 (56%), i.e. chronic headache (14%), chronic joint pain (12%), IBS (10%), and chronic back pain (9%). Only 47 (9%) had chronic organic diseases, i.e. diabetes, hypertension and bronchial asthma. Among females, 13% had menstrual cycle disturbances. More than half of participants reported that they visited the PHCC at least once in the past few months while 30% of them did not visit a PHCC during the last 12 months.

Table 3 depicts the rate of depression and GAD among participants. Depression was reported among 347 (68.9%), GAD affects 300 (59.5%), while 143 (28.4%) have both depression and GAD. The grades of depression were mild (31%), moderate (20%), and severe (19%) while that for GAD were mild (33.3%), moderate (17.3%), and severe anxiety 45 (8.9%).

Table 4 summarizes the association between some demographic data and moderate-severe depression and anxiety in this study. It is obvious that the rate of depression was high among females, illiterates, and housewives while GAD was high among women, illiterates and housewives also.

Moderate to severe depression affects 194 (38.5%) participants. It affects women 125 (44.0%), more than men 69 (31.4%) with a significant difference (x2 = 8.38, p-value = 0.004). Depression decreases in prevalence as a person has higher education, those who had intermediate or less had prevalence (47.1%), and those who had secondary school (43.7%), university (35.1%), and postgraduate (20%) with significant difference (x2 = 17.6, p-value = 0.007). Age groups were not significantly associated with depression or anxiety.

Moderate to severe anxiety affects 132 (26.2%) of participants. Women showed more anxiety compared to males (30.3%) versus (20.9%) with a significant difference (x2 = 5.63, p-value = 0.018). Also, anxiety prevalence decreased as a person had higher education, those who had secondary school or lower had prevalence (30.0%), whereas those who had graduated from university were (24.0%) with significant difference (x2 = 19.03, p-value = 0.004).

Table 1 : Socio-demographic characteristics of participants, Abha, KSA, 2017

Demographic character	No. (%)
Gender	
Male	220(44%)
Female	284(56%)
Nationality	
Saudi	489(96%)
Non-Saudi	15(4%)
Marital status	
Married	261(52%)
Single	225(44%)
Divorced	10(2%)
Widow	8(2%)
Educational status	
Illiterate	24(5%)
Primary-intermediate	46(9%)
Secondary	151(30%)
University	245(49%)
High education	38(7%)
Living status	
Own house	279(55%)
In rented house	157(31%
Not mentioned	68(14%)
Job	
Jobless	49(10%)
Housewife	88(18%)
Student	166(33%)
Governmental officer	123(24%)
Free work	11(2%)
Private sector	21(4%)
Retired	26(5%)
Others	20(4%)

Table 2: Utilization of PHCC services and common complaints among participants, Abha, KSA,2017

Item		No. (%)
Current complaints:		
No complaint		221(44%)
Physical complaints:		283(56%)
	chronic headache	*62(12%)*
	chronic joint pain	*47(9%)*
	chronic back pain	*15(3%)*
	chronic dizziness	*51(10%)*
	Irritable Bowel Syndrome	38(13%)
	menstrual cycle disturbance	47 (9%)
Chronic organic diseases:		
	hypertension	17(3%)
	diabetes	15(3%)
	bronchial asthma	13(2.6%)
	infertility	2(0.4%)
Visiting PHC during last year:		
	No visit	152(30%)
	1	86(17%)
	2	107(21%)
	3-4	163 (32%)

Table 3 : Prevalence of Depression and anxiety among participants, Abha, KSA,2017

		Depression PR=347(68.9%)				
	Grade Score	None	Mild (5-9)	Moderate (10-14)	Severe ≥15	Total
Anxiety PR= 300 (59.5%)	None ≤ 4	117	67	15	5	204
	Mild (5-9)	35	66	45	22	168 **(33.3%)**
	Moderate (10-14)	4	17	30	36	87 **(17.3%)**
	Severe ≥ 15	1	3	10	31	45 **(8.9%)**
	Total	**157**	**153 (31%)**	**100 (20%)**	**94 (19%)**	**504**

Table 4: Association between some participants' characteristics and moderate-severe depression and anxiety, Abha, KSA, 2017

	Depression		Anxiety	
Character	N (%)	X^2 (P-value)	n(%)	X^2 (P-value)
Gender				
Men	69 (31.4%)	$x^2 = 8.38$, p-value = 0.004	46 (20.9%)	$x^2 = 5.63$ p-value = 0.018
Women	124 (44.0%)		86 (30.3%)	
Marital status		$x^2 = 7.87$ p-value = 0.096		
Married	94 (36.0%)		67 (25.7%)	$x^2 = 4.11$ p-value = 0.39
Single	87 (41.2%)		58 (27.5%)	
Education status				
Illiterate	15 (71.4%)	$x^2 = 17.60$ p-value = 0.007	12 (57.1%)	$x^2 = 19.03$ p-value = 0.004
Elementary-intermediate	17 (37.0%)		9 (19.6%)	
Secondary	66 (43.7)		46 (30.5%)	
University	6 (19.4%)		62 (22.5%)	
Job				
Jobless	18 (38.3%)	$x^2 = 21.06$ p-value = 0.007	14 (29.8%)	$x^2 = 19.68$ p-value = 0.012
Housewife	44 (50.0%)		33 (37.5%)	
Students	67 (39.9%)		42 (25.0%)	
Government employee	38 (30.9%)		30 (24.4%)	
Others	21 (33.3%)		10 (15.9%)	

Discussion

This study revealed that more than two-thirds of the participants had depressive or/and anxiety with various severity. It reflects the magnitude of the high prevalence of the commonest two mental health problems, depression and anxiety disorders. It has consistencies with other recent studies conducted in the PHC centres. Therefore, this study augments the concept that, depression and anxiety has a role in the suffering of one to two-thirds of the population (2,3,8).

Table 2 represents that over half of participants complain of physical symptoms despite the absence of well-defined organic diseases, e.g. headache, LBP, joint pain, IBS with frequent visits to PHC centres. Compared with the prevalence of depression and anxiety in this study, we could conclude that depression and anxiety are playing a role behind the suffering of two-thirds of participants.

This study found that depression was significantly associated with female gender and higher educational level. In contrast, no association was found between depression and age group, gender, nationality, or marital status. However, severe depression was common among those with less education, jobless, divorced, and widowed.

In a study conducted among university students in Riyadh using PHQ9, the major depression was 9.9% (10). At the same time, in the Qassim region, Alharbi et al. found that moderate-severe depression and severe depression were 10.4% and 5% respectively among secondary school students with the high rate among females students (11). In a community-based study conducted by Alrashid et al. in Al-Hasa region, Saudi Arabia (12), a prevalence of 9.7% was reported and showed high rates among females, those with low educational status and jobless participants. Another study by Najeeb et al. which included 1,171 medical students from different regions in Saudi Arabia revealed that depressive symptoms were prevalent and vary from 23.4% with minimal symptoms to 17.8% with severe depressive symptoms and 6.3% had depressive diseases, and female students were affected more than males(13). In Malaysia, Kader et al(14) reported a prevalence rate of depression of 10.3%.

In this study, we found that the prevalence of moderately severe and severe GAD was 17% and 9% respectively. In a study conducted by AlHarbi, similar figures were reported, 19.5% and 9.8% respectively (11). While Mostafa et al. reported 14% among university students in Riyadh(10).

In Sweden, a community-based study which included 1,329 adults, reported a rate of GAD as 14.7 % (15) while in Malaysia, Kader et al. found the prevalence of anxiety was 8.2 % (16).

GAD was more prevalent among females, non-educated, housewives and participants who suffer from chronic headache, IBS or females with menstrual disturbance. The association regarding female gender was reported by Mostafa et al. and AlHarbi et al. also(10,11). The association between such variables and GAD could be explained as GAD has similar features of IBS, chronic headache and menstrual cycle-related symptoms. In this regard, patients with such problems should be assessed for GAD and managed accordingly.

Conclusion and Recommendation

This study revealed that the prevalence rates of depression and GAD among tourists are high, as among the general population. Many factors contribute significantly to the occurrence of depression and GAD, which should be identified and managed to relieve mental disorders symptoms. All opportunities such as summer heath campaign could be appropriately utilised to detect and to manage common mental disorders. PHQ-9 and GAD-7 are two simple tools that can be used to detect depression and GAD among the community and manage them earlier.

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Identifying depression symptoms among general population living in conflict zone in Jammu and Kashmir

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Abstract

Introduction: War is considered as one of the most horrifying human experiences. It is a complex, long lasting trauma composed of multiple stressors such as physical harm, intimidation, loss of loved ones, deprivation and abuse. Observations have depicted that over 2 billion people live in fragile conflict zones, driving 80% of the world's humanitarian needs. The symptoms of depression can include Feelings of helplessness and hopelessness, Loss of interest in daily activities, Appetite or weight changes, Sleep changes, Anger or irritability, Loss of energy.

The purpose of this study is to screen the symptoms of depression in the general population living in Srinagar which has been a conflict zone for the last 20 years. There is a need for intervention trials to establish evidence on mental health programs that have a positive impact on the mental health of the population in Jammu and Kashmir. It is hoped that there will be a greater commitment to the allocation of necessary resources for the development and trial of mental health interventions in the Kashmir Valley.

Objective: To Identify depression symptoms among the general population living in q conflict zone in Srinagar, Jammu and Kashmir

Material and Methods: A Cross-sectional study was conducted on a sample of 480 participants from various sections of society living in Srinagar, Kashmir. The study was conducted for a period of four months from January 2019 to April 2019.The Data was collected from Sher E Kashmir Institute Of Medical Sciences , Islamic University of Science and Technology and University of Kashmir; all three are located in Srinagar, Jammu and Kashmir. The sample was taken through Non-Probability Purposive Sampling. A pre–structured questionnaire which was a modified Hopkins Symptoms Checklist (HSCL-IV) was distributed among the participants. A Pilot study was conducted to assess the authenticity of the questionnaire. Data collected was entered and analyzed using SPSS version 20, with 95% confidence interval. All Ethical considerations were observed.

Results: Regarding the age distribution, 67.7% of participants were aged 18 to 25 years, 21.7% aged 26 to 35 years, 7.3% aged 36 to 45 years, 2.5% aged 46 to 60 years and 0.6% aged more than 60 years. About 50.2% of participants were male and 49.8% were female. With respect to the participants' place of residence, 78.5% of participants were from Srinagar, 6.9% were from Pulwama, 4.8% were from Shopian and Kulgam, 2.7% were from Anantnag and 2.3% were from Badgam. The level of education distribution depicted about 0.6 % were not formally educated , 0.8% had studied up until Primary, 2.9 % were matriculates, almost 46% were intermediate, 34.4 % had done their graduation and 15.2 had studied up until post graduate level. Regarding their marital status, 74.6 % were married and 25.4% were unmarried. 27.3% had an extended family set up while 72.7% had a nuclear family type of set up. With respect to the participants' responses of Hopkins Symptoms Checklist, 93.1% had trouble keeping their mind on things that they did. 84.8% had more trouble with their memory than usual. 77.7% felt unusually tired

every day. 74.2% found it hard to enjoy life. Of all the participants, 71.3% had a lot of different physical symptoms or unusual pains and 71.1% had been feeling emotionally numb, not caring, sad, unhappy or miserable. 71.3 % responded that they had been feeling more pessimistic or negative than usual whereas 70.2% said that they had lost interest or enjoyment in the things they normally did. 74.4% responded that they had been less motivated, less productive, or found it more difficult to cope than usual . 73.1% had been sleeping worse than usual. 68.5% responded that they had been less interested in talking to people or mixing with people than usual whereas another 68.5% also responded that they been more worried, nervous or uptight than usual. Among the participants, 71.5% had been more easily tearful, or crying more than usual. 67.5% had enjoyed their food less than usual. 59.4 % of the participants responded that their sexual interest had been less than usual. 75.8% had been less self-confident than usual. 76.7% had been more easily annoyed or more impatient than usual. To 71.5%, life seemed meaningless and 44.4% responded yes when asked whether dying looked like a good option.

Conclusion: The ongoing regional conflict in Jammu and Kashmir has resulted in widespread prevalence of symptoms of depression in the general population. There is an immediate need of starting interventional programs for early diagnosis and prompt treatment of a highly vulnerable population residing in a decades old conflict zone.

Key words: depression +symptoms+ conflict zone+ Intervention

Introduction

Globally, psychological disorders make up a large proportion of disease burden and are recognized as the leading cause of years of life lived with a disability (Disability-Adjusted Life Years) (1). War is considered as one of the most horrifying human experiences. It is a complex, long lasting trauma composed of multiple stressors such as physical harm, intimidation, loss of loved ones, deprivation and abuse (2). Observations have depicted that over 2 billion people live in fragile conflict zones, driving 80% of the world's humanitarian needs. These complex crises threaten efforts to end extreme poverty, and often increase tensions between ethnic, tribal and political groups. Resulting instability and threats of violence drive people from their homes and prevent access to food, water, health services and shelter (3).

Various conducted studies have shown that exposure to conflict-related potentially traumatic events (PTE) will lead to an elevation in the prevalence of mental disorders, including depression and post-traumatic stress disorder (PTSD), among exposed sections of the population(4).

Little is known about the impact of traumatic experiences and stressful life conditions on people in low-income countries who live in conditions of ongoing political violence.

Depression is a mood disorder that causes a persistent feeling of sadness and loss of interest. Also called major depressive disorder or clinical depression, it affects how you feel, think and behave and can lead to a variety of emotional and physical problems. You may have trouble doing normal day-to-day activities, and sometimes you may feel as if life isn't worth living(5).

Post Traumatic Stress Disorder and Major Depression affects women more frequently than men. While women tend to respond to traumatic stress by under modulation of emotions and low self-esteem, men tend to respond by over modulation of emotions. Rather than being a derivative of sex differences, this complementary diversity in response types between genders seems to be shaped by social factors in consideration of survival under extreme threat(6).

The experience of torture places the survivors at a heightened risk for somatic and mental health problems(7).

A study conducted in Columbia, demonstrates a clear impact of the conflict on mental health. Among those who consulted with mental health professionals, specific conflict characteristics could predict symptom profiles. However, some of the highest risk outcomes, like depression, suicide risk and aggression, were more related to factors indirectly related to the conflict. This suggests a need to focus on the systemic effects of armed conflict and not solely on direct exposure to fighting(8).

A study conducted in Jammu and Kashmir examined the prevalence of posttraumatic stress disorder (PTSD) symptoms, depression, and coping mechanisms among the adult civilian population in Indian Kashmir(9).

Mental health is an integral part of overall health and quality of life. Effective evidence-based programs and policies are available to promote mental health, enhance resilience, reduce risk factors, increase protective factors, and prevent mental and behavioral disorders. Innovative community-based health programs which are culturally and gender appropriate and reach out to all segments of the population need to be developed. Substantial and sustainable improvements can be achieved only when a comprehensive strategy for mental health which incorporates both prevention and care elements is adopted(10).

Conflict exposure and total perceived social support were significantly associated with an increase in Post Traumatic Stress Disorder. Formulation of programs to sensitize

people living in conflict zones about the importance of Post Traumatic Stress Disorder and social support in buffering negative outcomes can help lessen their stress, increase their ability to withstand adversities and help them move towards personal growth(11).

According to a study conducted in Syria the ongoing hardships and violence associated with the conflict in Syria have had pervasive effects on the mental health and psychosocial wellbeing of adults and children, both among those internally displaced and those seeking asylum. For refugees, experiences related to the conflict are compounded by the daily stressors of resettlement in a new country, which include language barriers, poverty, lack of resources and services to meet basic needs, difficulty accessing services, risks of violence and exploitation, discrimination and social isolation(12).

There is an essential need for implementation of mental health awareness programs, interventions aimed at high risk groups and addressing trauma-related symptoms from all causes in Kashmir Valley(13).

The symptoms of depression can include Feelings of helplessness and hopelessness, Loss of interest in daily activities, Appetite or weight changes, Sleep changes, Anger or irritability, Loss of energy(14).

The purpose of this study is to screen the symptoms of depression in the general population living in Srinagar which has been a conflict zone for the last 20 years. There is a need for intervention trials to establish evidence on mental health programs that have a positive impact on the mental health of the population in Jammu and Kashmir In response to the findings of another study conducted in the region in 2017 (15). It is hoped that there will be a greater commitment to the allocation of necessary resources for the development and trial of mental health interventions in the Kashmir Valley.

Study Objective

To Identify depression symptoms among the general population living in the conflict zone In Srinagar, Jammu and Kashmir

Methodology

A Cross-sectional study was conducted on a sample of 480 participants from various sections of society living in Srinigar, Kashmir. The study was conducted for a period of four months from January 2019 to April 2019. The Data was collected from Sher E Kashmir Institute Of Medical Sciences , Islamic University of Science and Technology and University of Kashmir; all three are located in Srinagar, Jammu And Kashmir. The sample was taken through Non-Probability Purposive Sampling. The data was collected with extreme caution regarding personal safety of data collectors. A pre – structured questionnaire which was modified Hopkins Symptoms Checklist (HSCL-IV) was distributed among the participants. Questions asked were related to age, gender, education, marital status, occupation, generalized emotional status, factors influencing their mental health, anxiety and nervousness. A Pilot study was conducted to assess the authenticity of the questionnaire. Data collected was entered and analyzed using SPSS version 20, with 95% confidence interval. All Ethical considerations were observed.

Results

Table 1 gives an outlook of participants' demographic profile. Regarding the age distribution, 67.7% participants were aged 18 to 25 years, 21.7% aged 26 to 35 years, 7.3% aged 36 to 45 years, 2.5% aged 46 to 60 years and 0.6% aged more than 60 years. About 50.2% participants were male and 49.8% were female. With respect to the participants place of residence, 78.5% of participants were from Srinagar, 6.9% were from Pulwama, 4.8% were from Shopian and Kulgam, 2.7% were from Anantnag and 2.3% were from Badgam. The level of education distribution depicted about 0.6 % were not formally educated, 0.8% had studied up until Primary, 2.9 % were matriculates, almost 46% were intermediate, 34.4 % had done their graduation and 15.2 had studied up until post graduate level. Regarding their marital status, 74.6 % were married and 25.4% were unmarried. 27.3% had an extended family set up while 72.7% had a nuclear family type of set up. With respect to the participants' responses of Hopkins Symptoms Checklist, 93.1% had trouble keeping their mind on things that they did. 84.8% had more trouble with their memory than usual. 77.7% felt unusually tired every day. 74.2% found it hard to enjoy life. Of all the participants, 71.3% had a lot of different physical symptoms or unusual pains and 71.1% had been feeling emotionally numb, not caring, sad, unhappy or miserable. 71.3 % responded that they had been feeling more pessimistic or negative than usual whereas 70.2% said that they had lost interest or enjoyment in the things they normally did. 74.4% responded that they had been less motivated, less productive, or found it more difficult to cope than usual . 73.1% had been sleeping worse than usual. 68.5% responded that they had been less interested in talking to people or mixing with people than usual whereas another 68.5% also responded that they been more worried, nervous or uptight than usual. Among the participants, 71.5% had been more easily tearful, or crying more than usual. 67.5% had enjoyed their food less than usual. 59.4 % of the participants responded that their sexual interest had been less than usual. 75.8% had been less self-confident than usual. 76.7% had been more easily annoyed or more impatient than usual. To 71.5%, life seemed meaningless and 44.4% responded yes when asked whether dying looked like a good option.

Table 1:Demographic profile

S No	Variable	Parameter	Frequency	Percentage
1	Age	18-25 years	325	67.7
		26-35 years	104	21.7
		36-45 years	35	7.3
		46-60 years	12	2.5
		> 60 years	3	0.6
2	Gender	Male	241	50.2
		Female	239	49.8
3	Residence	Srinagar	377	78.5
		Badgam	11	2.3
		Shopian	23	4.8
		Pulwama	33	6.9
		Anantnag	13	2.7
		Kulgam	23	4.8
4	Level of Education:	Not formally educated	3	0.6
		Primary	4	0.8
		Matriculate	14	2.9
		Intermediate	221	46
		Graduate	165	34.4
		Post graduate	73	15.2
5	Marital status:	Married	358	74.6
		Unmarried	122	25.4
6	Family type:	Extended	131	27.3
		Nuclear	349	72.7

Figure 2: Psycho-social impact

Item No	Item	Response	Frequency	Percentage
1	Have you had trouble keeping your mind on things you were reading, or watching on television?	• Yes • No	447 33	93.1 6.9
2	Have you had more trouble with your memory than usual?	• Yes • No	407 73	84.8 15.2
3	Have you been feeling unusually tired every day?	• Yes • No	373 107	77.7 22.3
4	Have you found it hard to enjoy life?	• Yes • No	356 124	74.2 25.8
5	Have you had a lot of different physical symptoms or unusual pains?	• Yes • No	342 138	71.3 28.7
6	Have you been feeling emotionally numb, not caring, sad, unhappy or miserable?	• Yes • No	344 136	71.1 28.3
Item No	Item	Response	Frequency	Percentage
7	Have you been feeling more pessimistic or negative than usual?	• Yes • No	342 138	71.3 28.7
8	Have you lost interest or enjoyment in the things you normally do?	• Yes • No	337 143	70.2 29.8
9	Have you been less motivated, less productive, or found it more difficult to cope than usual?	• Yes • No	357 123	74.4 25.6
10	Have you been sleeping worse than usual?	• Yes • No	351 129	73.1 26.9
11	Have you been less interested in talking to people or mixing with people than usual?	• Yes • No	329 151	68.5 31.5
12	Have you been more worried, nervous or uptight than usual?	• Yes • No	329 151	68.5 31.5
13	Have you been more easily tearful, or crying more than usual?	• Yes • No	343 137	71.5 28.5
14	Have you enjoyed your food less than usual?	• Yes • No	324 156	67.5 32.5
14	Has your sexual interest been less than usual?	• Yes • No	285 195	59.4 40.6
15	Have you been less self-confident than usual?	• Yes • No	364 116	75.8 24.2
16	Have you been more easily annoyed or more impatient than usual?	• Yes • No	368 112	76.7 23.3
17	Has life seemed meaningless?	• Yes • No	343 137	71.5 28.5
18	Has dying looked like a good option?	• Yes • No	213 267	44.4 55.6

Figure 1:

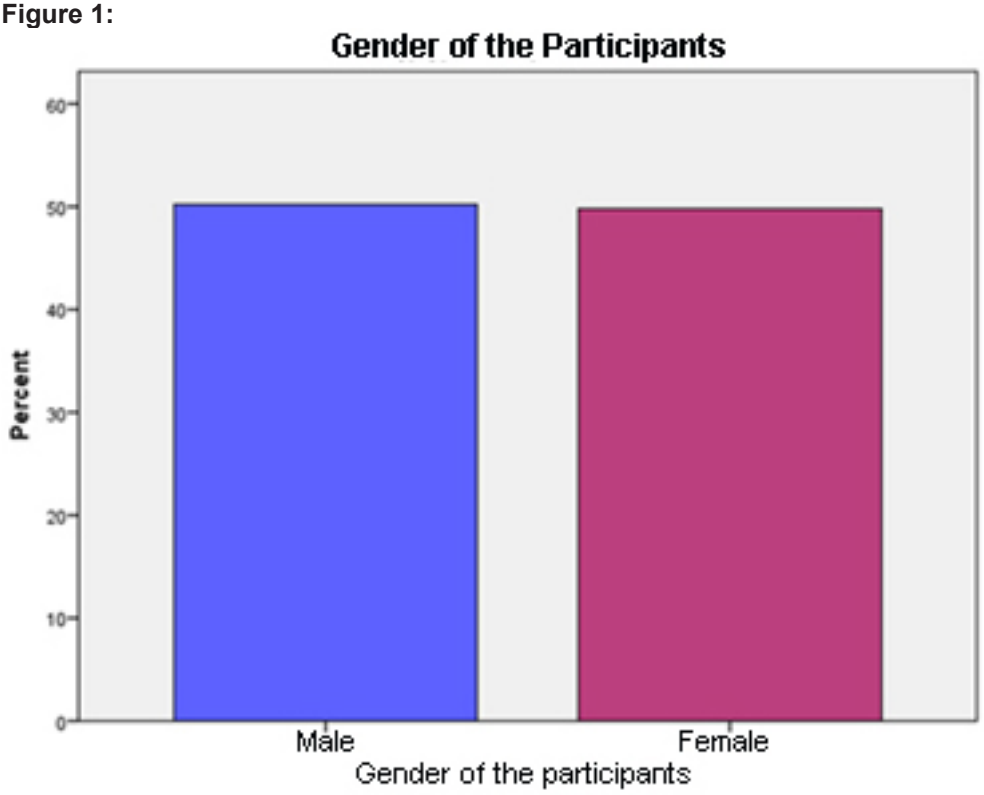

Figure 1 shows that 50.2% (n=241) of the participants were male and 49.8% (n=239) of the participants were female

Figure 2:

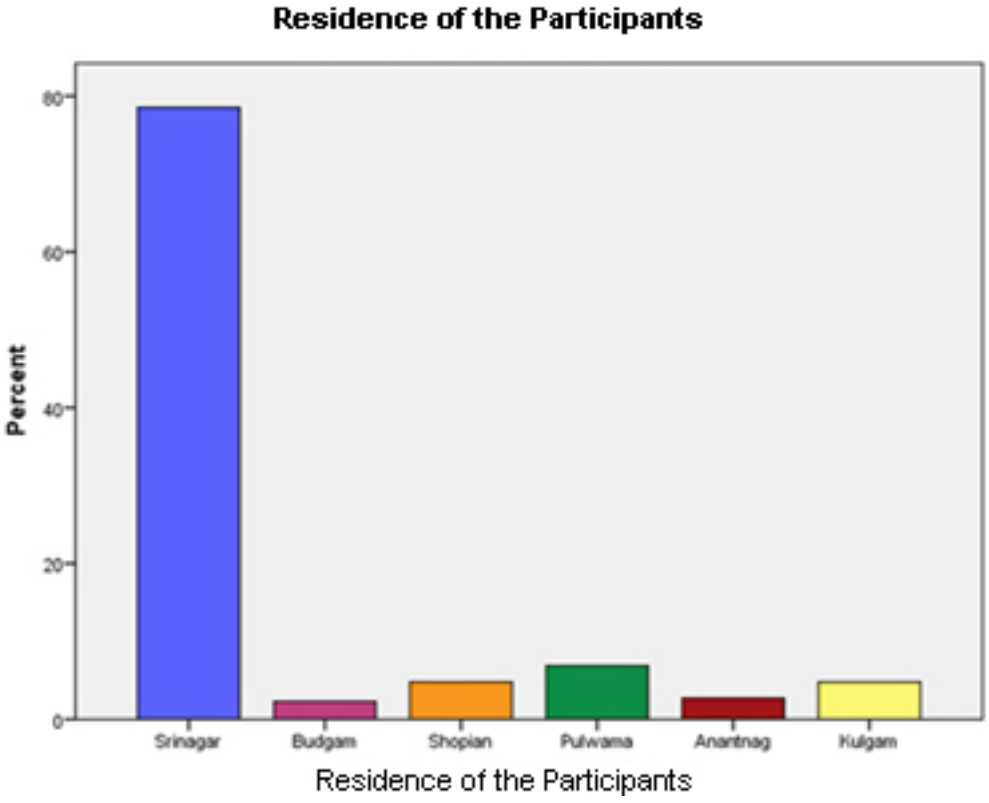

Figure 2 shows that 78.5% (n=377) of participants were from Srinagar, 2.3% (n=11) were from Badgam , 4.8% (n=23) were from Shopian , 6.9% (n=33) were from Pulwama, 2.7% (n=13) were from Anantnag and 4.8% (n=23) were from Kulgam .

Figure 3:

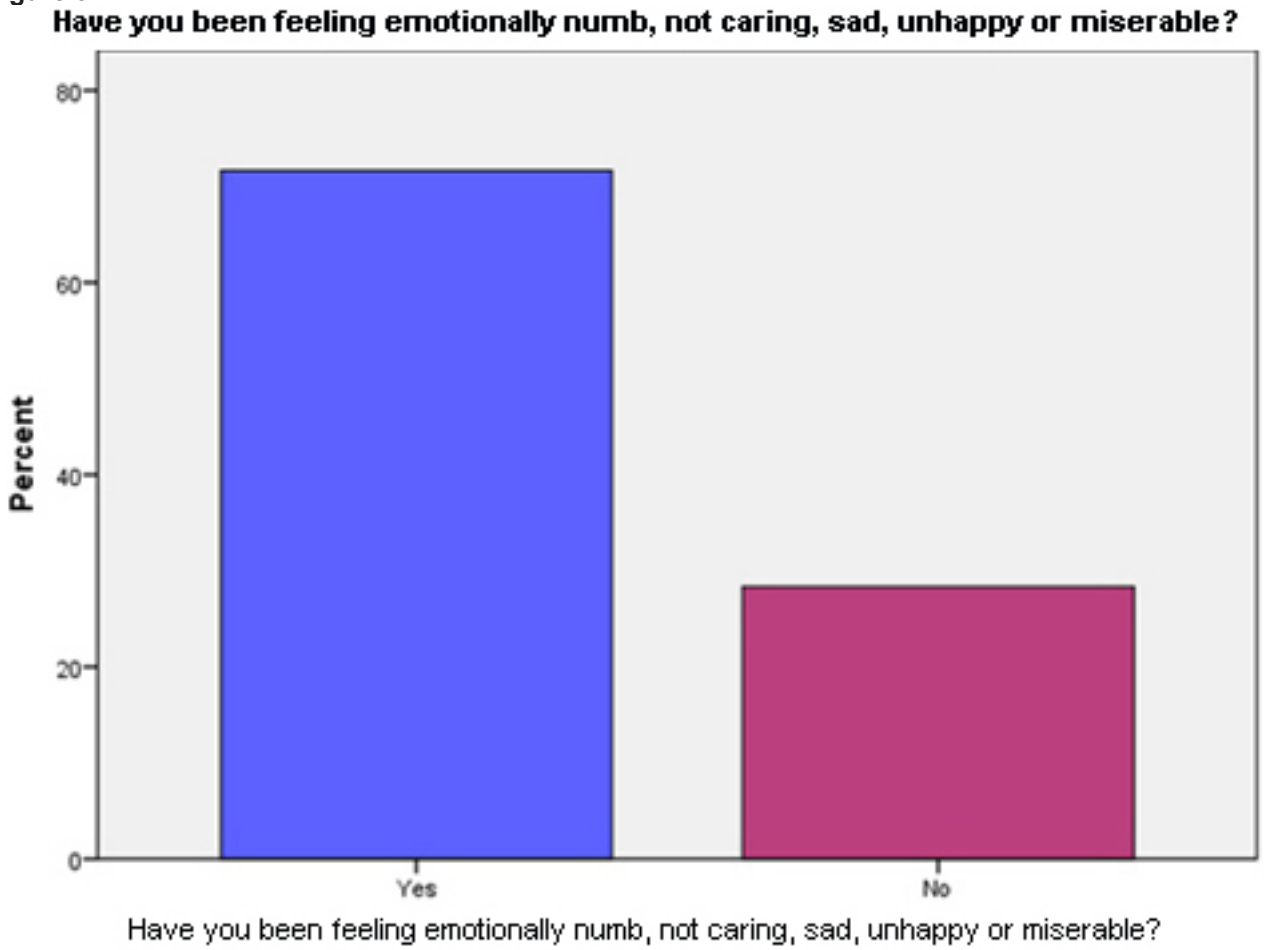

Figure 3 showing that 71.1% (n=344) said yes when asked whether they had been feeling emotionally numb, not caring, sad, unhappy or miserable. Only 28.3 % (n=136) said no when asked the same question.

Figure 4:

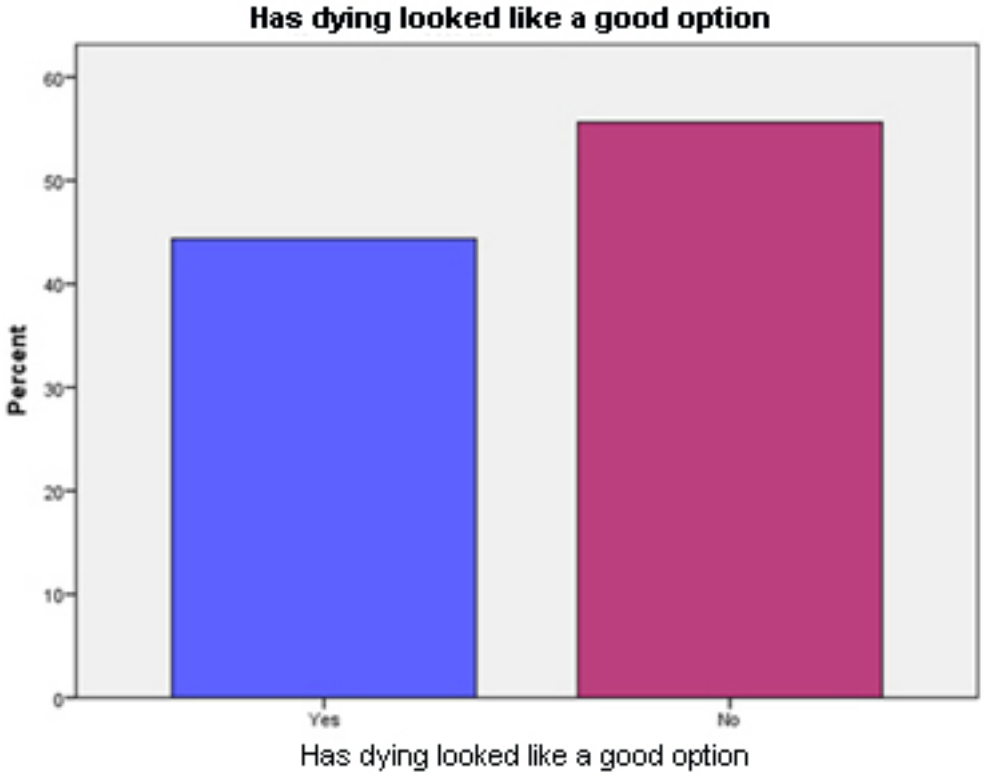

Figure 4 showing that when asked whether dying looked like a good option, almost 44.4% (n=213) responded yes and 55.6% (n=267) said no to the same question.

Discussion

The continuous ongoing military conflict has had its physical and mental toll on the general population of Jammu and Kashmir. According to a study conducted in 2011 in Libya the findings presented in that paper highlight the potential magnitude of the post-conflict mental health need in Libya, a model that can also be applied to other countries experiencing such conflict. Mental health problems are already surfacing, according to reports from mental health teams on the ground (16). Perhaps unsurprisingly, the evidence to date suggests that armed conflict has a powerful negative effect on the mental health of civilians. The majority of this evidence comes from retrospective studies that report a clear association between mass violence and poor long-term psychological outcomes in adult civilians from Afghanistan (17).

Due to a similar conflict situation, the general population is facing a tremendous amount of mental stress in Jammu and Kashmir. When the participants were asked whether they found it hard to enjoy life, 74.2% of the participants responded with an affirmative. This analysis of data from civilians was similar to a study conducted in Columbia. (18). The repeated exposure to traumatic events results in symptoms like withdrawal,

Emotional numbness, detachment, intrusion in the form of flashbacks and nightmares, hyperactivity etc. can trigger these feelings as was confirmed by another study conducted in Kashmir(19).

In this study, of all the participants, 71.3% had a lot of different physical symptoms or unusual pains and 71.1% had been feeling emotionally numb, not caring, sad, unhappy or miserable. Similar findings were observed on a group of Bhutanese refugees fleeing a conflict zone in Bhutan, with victims of torture likely to present with PTSD, persistent somatoform pain disorder, affective disorders, generalized anxiety disorder, and dissociative symptoms(20).

In this study, to 71.5% life seemed meaningless and 44.4% responded yes when asked whether dying looked like a good option. For the general population 44.4% responded affirmative to the question of dying as an option is extremely disturbing and alarming. Similar findings were noted during a study conducted in Colombia which showed a clear risk for suicide in conflict affected civilian populations. Colombia has a one of the highest rates of suicide risk behavior in the world (21).

Conclusion

The ongoing regional conflict in Jammu and Kashmir has resulted in widespread prevalence of symptoms of depression in the general population. There is an immediate need of starting interventional programmes for early diagnosis and prompt treatment of a highly vulnerable population residing in a decades old conflict zone.

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Knowledge, Attitude and Practice of Stethoscope Disinfection among Health Care Providers in Karachi

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Abstract

Introduction: The stethoscope has been found to be a potential vector for spreading nosocomial infection all over the world. Most commonly contamination of stethoscope occured when medical practitioners used the same stethoscope to auscultate many patients without disinfection. Strict adherence to stethoscope disinfection practices by health workers can minimize cross-contamination and ensure improved patient safety in hospital environments. This study was carried out to assess the knowledge, attitude and practices regarding stethoscope disinfection among students, trainee and residents doctors at Jinnah Postgraduate Medical Center.

Methodology: This was a cross sectional study, conducted among medical students, trainee and resident doctors of Jinnah Sindh Medical University and Jinnah Postgraduate Medical Centre respectively from July 2019 to December 2019. Sample size calculated for the study was 316. Data was collected by circulating a self-administered questionnaire made after careful literature review. Data was analyzed using SPSS version 20.0 and descriptive analysis was performed.

Result: Among the study participants 174(55.02%) had never cleaned their stethoscope. A lot of respondents 257(81.3%) thought stethoscope as a potential vector for infection. The majority 135(42.7%) considered diaphragm was the most commonly infected part. A lot of participants 145(45.9%) thought that Methicillin Resistant Staphylococcus Aureus (MRSA) could spread through stethoscope. Alcohol swab was regarded as the most suitable disinfectant for sterilization of stethoscope by 260(82.2%) participants.

Conclusion: Our study concluded that there is a lack of practice by medical providers to disinfect their stethoscope in spite of considering stethoscope as a potential vector for nosocomial infection. Therefore measures should be taken to elevate practice of stethoscope disinfection to reduce the nosocomial infection effectively.

Key words: Stethoscope, Disinfection, Cross Infection.

Introduction

In medical practice the most commonly used instrument is the stethoscope. Contamination of stethoscope with infective microorganism is very common due to aberrant contact with huge number of patients(1). Stethoscope has been found to be a potential vector for spreading nosocomial infection all over the world(2). During auscultation stethoscope contamination is common; if the same stethoscope is used for the next patient without disinfection, it might bring risk of infection to the patient and may continuously impose the risk serially to all patients(3). It is estimated that every year directly 19,000 and indirectly 80,000 deaths occur because of hospital acquired infections(4). In every 100 admitted patients, 5-10 patients acquire nosocomial infection annually(5). Recent work has shown that contamination of stethoscope diaphragms could be 100%(6).

The most frequent microorganisms obtained from stethoscope are Methicillin Resistant Staphylococcus Aureus [MRSA], Pseudomonas species, Clostridium difficile, Escherichia coli and Vancomycin Resistant Enterococci(1,7,8). Most commonly contamination of stethoscope occurred when medical practitioners used the same stethoscope to auscultate many patients without disinfecting it(9). Stethoscope contact with infected skin such as near colostomy openings, sternotomy wounds and onto the chest of newborn without disinfection can result in colonization of pathogenic bacteria residing on the diaphragm of the stethoscope(10). It has been noted that there is great significance of disinfecting a stethoscope. In some settings it has been observed that students, doctors and residents clean their stethoscope after every clinical procedure or examination(11). Strict adherence to stethoscope disinfection practices by health workers can minimize cross-contamination and ensure improved patient safety in hospital environments(12).

Isopropyl alcohol has been found to be the most common disinfectant used to disinfect stethoscopes by health care providers. It has been reported that alcohol kills 94% of bacteria on the stethoscope diaphragm in contrast to antiseptic soap, removing 74% bacteria on diaphragm. Remarkable variation has been found in frequency of stethoscope disinfection(10). Results show significant reduction in bacterial counts after cleaning with 70% isopropyl alcohol. Hence cleaning with alcohol based swabs or at least one of the disinfectants or hand sanitizers should be used to ensure reduction in the number of microbes after consulting/use of stethoscope to avoid nosocomial infections (13). According to a study conducted in Greece the findings supported the evidence that Stethoscope contamination following a single physical examination is not negligible and is associated with a level of contamination of the patient's skin(14). Prevention of pathogen dissemination is needed. Frequency of disinfecting stethoscope has been found to decrease bacterial growth on stethoscope diaphragm and in that way could minimize spread of hospital acquired infection(5).

Therefore this study was carried out to assess knowledge, attitude and practice of residents, doctors and students regarding stethoscope disinfection at Jinnah Postgraduate Medical Center and Sindh Medical University, Karachi.

Materials and method

This was a cross-sectional study, conducted at Jinnah Postgraduate Medical Center and Sindh Medical University, Karachi from July 2019 till December 2019. A total of 316 participants were included in the study using Non-probability convenience sampling technique. All students of Third, Fourth, Final Year MBBS studying at Sindh Medical College, House officers and Trainee residents posted in different wards at Jinnah Postgraduate Medical Centre, Karachi irrespective of gender and age were included. All those not willing to participate in the study were excluded.

The data was collected by circulating a structured questionnaire among the study participants. The questionnaire was validated through a pilot study done on 30 participants and Cronbach's Alpha value was also calculated which was found to be 0.75. The questionnaire was comprised of three parts. The first part consisted of questions assessing knowledge of the participants regarding stethoscope disinfection, the second part included questions determining their attitude and the third part was formulated to determine stethoscope hygiene practices of the medical students, doctors and residents. Written and verbal informed consent was taken from all the participants. Prior approval from the college ethical committee was also obtained.

Data collected was analyzed using IBM SPSS V 20.0. Descriptive analysis was done for the variables. Quantitative data was presented in mean and standard deviation while qualitative data was presented in frequencies and percentages.

Source of funding: We did not receive any type of funding in any form for the study.

Result

In our conducted study, total respondents were 316. Among them, 158 (50%) were students, 79 (25%) were house officers and 79 (25%) were trainee residents (see Figure 1). When asked about awareness regarding stethoscope cleaning protocol, 165 (52.2%) said they did not know while 151 (47.8%) responded in the positive. Among those who replied yes, the majority, 59 (39.0%) were students, 54 (35.8%) were house officers and 38 (25.2%) were trainee residents. Many participants 235 (74.4%) considered sanitizing and disinfecting the stethoscope as disinfection of stethoscope while 44 (13.9%) did not know what it meant. Others also saw heating 33 (10.4%) and washing 4 (1.3%) as stethoscope disinfection. Talking about parts of the stethoscope getting infected, 135 (42.7%) thought the diaphragm was the most commonly infected part. Ear piece 60 (19%), bell 36(11.4%), whole

stethoscope 27 (8.5%) and tubing 26 (8.2%) were the other parts viewed to being infected by other participants. People who thought the diaphragm as the part to be infected most frequently included the majority of students 72 (41.9%), trainee residents 53 (30.8%) and 47 (27.3%) house-officers. Alcohol swab/propyl alcohol was thought to be the most suitable disinfectant by the majority 260 (82.3%) of those taking part. Other disinfectants thought useful were hand-sanitizers 26 (8.2%), soap 3 (1.0%) and cloth 10 (3.2%). The majority of respondents 259 (82.0%) believed the stethoscope to be a potential vector of infection while others 57 (18%) had an alternative opinion. Among the participants the majority of the students 142 (44.9%), house-officers 68 (21.5%) and trainee residents 66 (20.8%) believed that regular cleaning of stethoscope would result in reducing nosocomial infections. On the other hand 16 (5.1%) students, 12 (3.8%) trainee residents and 12 (3.8%) house-officers thought otherwise. A lot of participants 145 (45.9%) thought that MRSA could spread through stethoscope while in others' opinion Clostridium Difficile 7 (2.2%), Escherichia Coli 31 (9.8%), Pseudomonas Aeruginosa 21 (6.6%) could also spread and 112 (35.4%) opted that they did not know about it. Regarding importance of stethoscope cleaning an overwhelming number of the participants 305 (96.5%) responded in agreement contrary to only 11 (3.5%) who regarded it as unimportant. The majority of the participants 295 (93.3%) considered stethoscope cleaning a good practice, 10 (3.1%) regarded it as time consuming and 7 (2.2%) thought it as harmful. Masses of students 172 (54.4%), house-officers 73 (23.1%) and trainee residents 74 (23.4%) recommended that stethoscopes should be cleaned/disinfected.

Among the respondents the majority of the students 98/158 (62%) and house-officers 41/79 (51.9%) had never cleaned their stethoscopes. In contrast the majority of trainee residents 43/79 (54.4%) claimed to clean their stethoscopes. Among the respondents who never cleaned their stethoscope, 146 (46.2%) gave no response as to why they don't clean their stethoscopes, 113 (35.7%) said that they don't know how to clean their stethoscope, 43 (13.6%) replied they don't get time to do it, 8 (2.5%) considered it a useless practice and 6 (1.8%) believed that it would damage their stethoscope. When asked which part of the stethoscope they clean the majority 117 (37%) of the respondents answered diaphragm (see Table 1). Most of the participants 157 (49.6%) claimed that they use alcohol swab for stethoscope disinfection. This was followed by 46 (14.5%) of the participants using hand sanitizer, cloth being selected by 19 (6.01%) and soap was picked by 10 (3.16%) for disinfecting purpose. Regarding how frequently the participants clean their stethoscope a large number of students 32 (10.1%), house-officers 16 (5.1%) and trainee residents 31 (9.8%) responded when they get time to clean their stethoscopes. Disinfection of stethoscope after each examination was reported by 17 (5.4%) students, 11 (3.5%) house-officers and 4 (1.3%) trainee residents. Stethoscope was cleaned after every shift by 6 (1.9%) students, 9 (2.8%) house-officers and 4 (1.3%) trainee residents. Few of the house-officers 7 (2.2%), students 11 (3.5%) and trainee residents 5 (1.6%) said that they don't remember the last time they cleaned their stethoscopes. Interestingly a lot of students 92 (29.1%), house-officers 36 (11.4%) and trainee residents 34 (10.8%) opted not to give any response to this question also (see Figure 2).

Most of the participants 305 (96.5%) uttered that they have never attended any awareness program regarding stethoscope disinfection while 11 (3.5%) claimed that they had attended such programs. For arranging awareness sessions regarding stethoscope disinfection, 301 (95.2%) of the participants were in favor while remaining 15 (4.8%) were against. The majority of the participants 300 (94.9%) reported that they were not provided with any material for disinfecting stethoscope while 16 (5.1%) responded in affirmation.

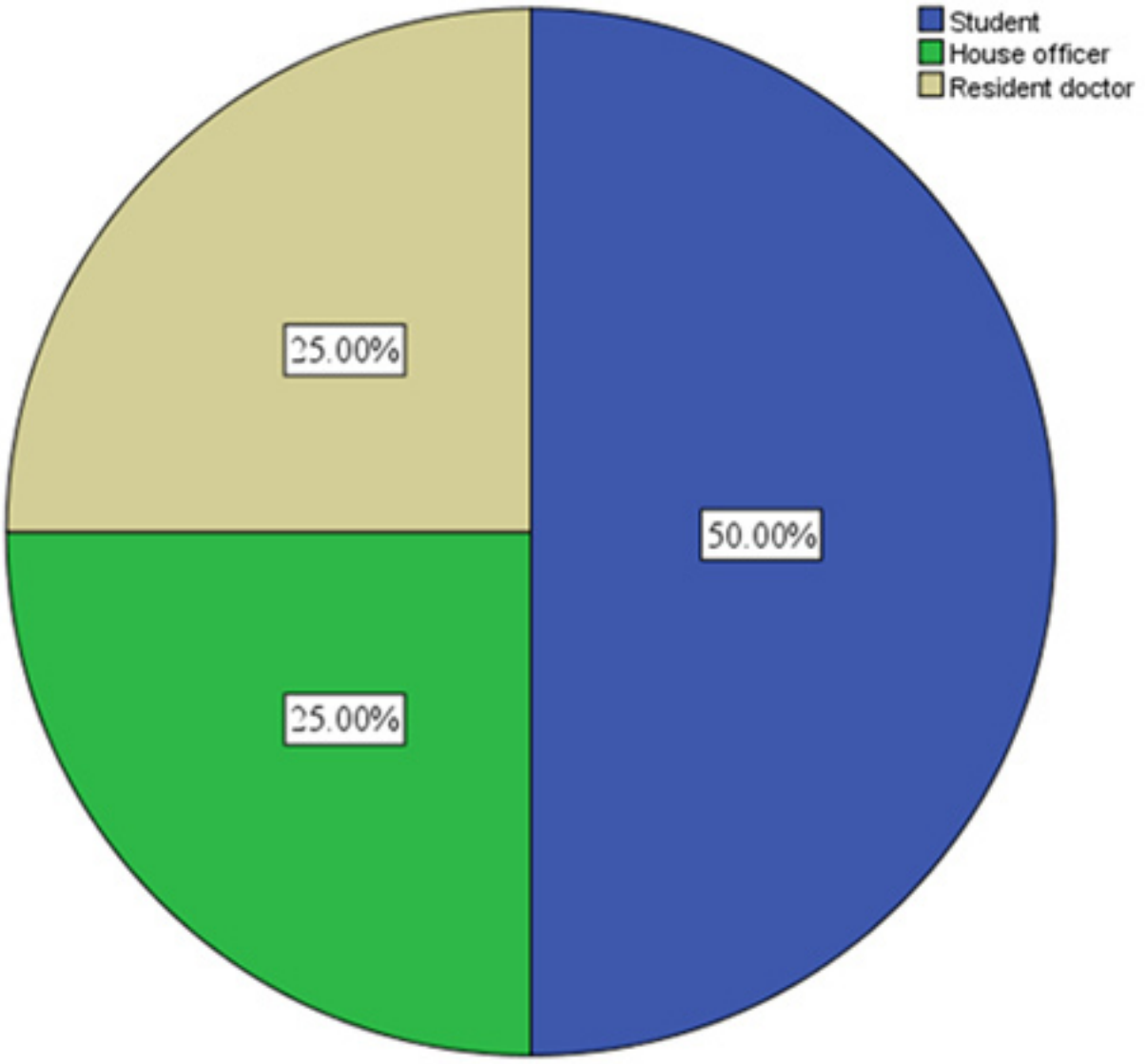

Figure 1: Designation of participants

Part of stethoscope	Students (N, %)	House officers (N, %)	Trainee residents (N, %)
Diaphragm	47(29.7%)	36(45.6%)	34(43%)
Bell	16(10.1%)	10(12.6%)	11(13.9%)
Tubing	2(1.3%)	2(2.5%)	6(7.6%)
Ear pieces	21(13.3%)	11(14.0%)	5(6.3%)
Whole stethoscope	23(14.6%)	12(15.2%)	9(11.4%)
No response	49(31.0%)	8(10.1%)	14(17.7%)

Table 1: Disinfection of different parts of stethoscope

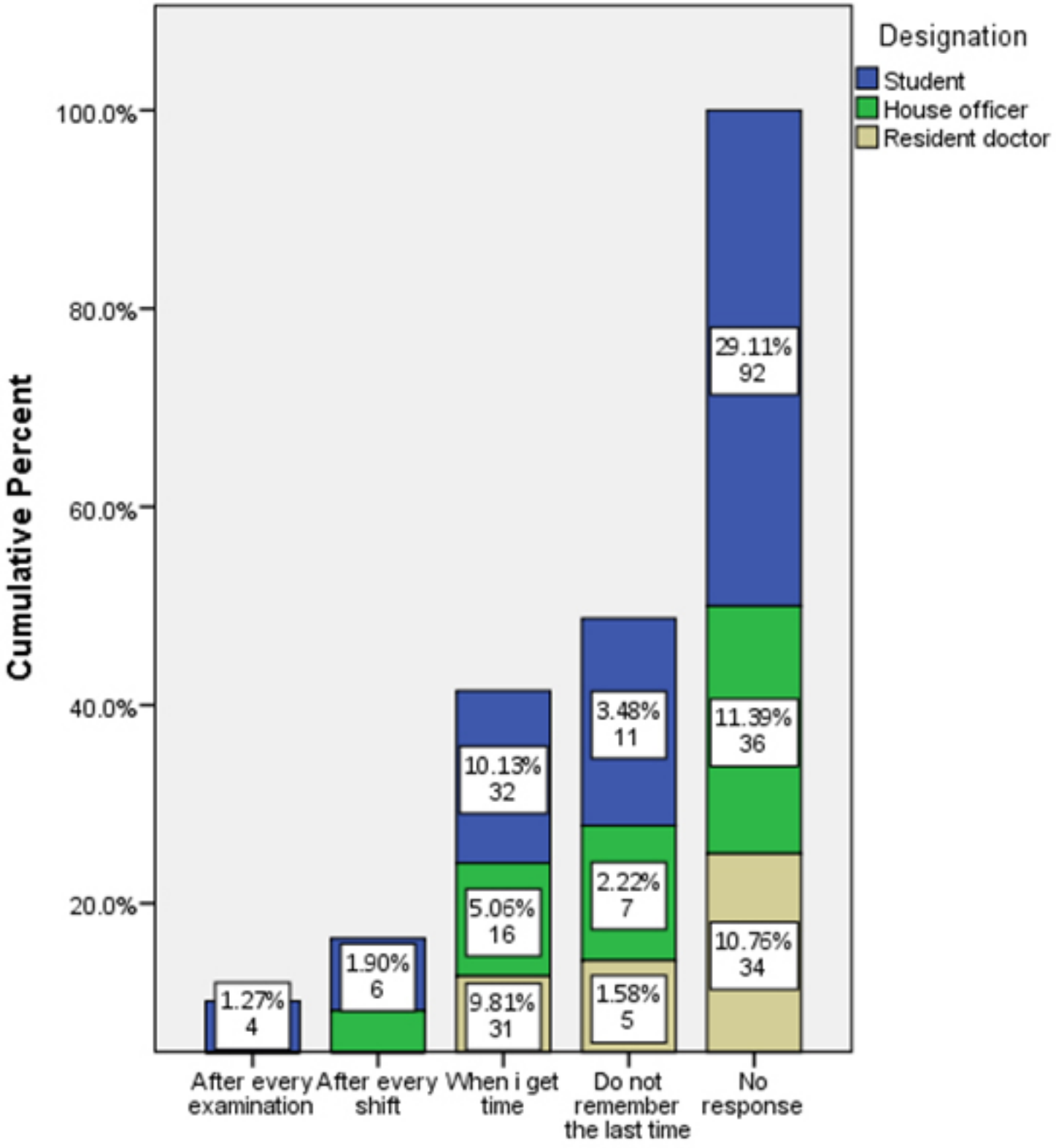

Figure 2: Frequency of stethoscope disinfection

Discussion

The stethoscope is weighed as the most important and basic clinical instrument used by medical professionals in examining patients. Several studies have highlighted that stethoscope is a potential vector for spread of health-care associated infection(1,2,5,9–11). Our study reported that 80% or more of participants believed that stethoscope is the major source for transmitting nosocomial infection among patients.

This study revealed that the percentage of doctors who had never cleaned their stethoscope was 48.4%. Our results are far worse than studies from India and Saudi Arabia where only 16% and 12% of doctors had claimed to never cleaned their stethoscopes(5, 15). A study from Baghdad had shown poorer results than ours with 58% of the doctors who had never cleaned their stethoscopes(10). In this present study 51.59% of doctors and 60% of students had claimed to disinfect their stethoscopes. This finding was better than a study conducted in Bengal which stated that a considerably low number (16%) of doctors and none of the medical students had cleaned their stethoscope ever(16). Our results were also superior to the study conducted in Rawalpindi which showed 37.7% of doctors had ever cleaned their stethoscopes(16). On the other hand, Fourth and Sixth Year Serbian medical students had reported a very high percentage of 79.8% and 81.8% respectively for students who cleaned their stethoscopes(1). This percentage of students stating they cleaned their stethoscope is higher than our study participant students. Whittington et al in London showed that 91% of Health Care Workers disinfected their stethoscope after every use(3). In contrast to Whittington study results, our study reflected that the participants who cleaned their stethoscope after every patient contact was very low (10.1%). The reason for this could be lack of awareness about stethoscope disinfection among students and doctors as is also reported in our study. Another reason for this result might be that consultants in teaching hospitals are not practicing stethoscope disinfection after every examination. Diaphragm was the part which was most commonly disinfected by our study participants. A study conducted by Gazibara et al also conveyed that the majority of participants cleaned their diaphragms as a part of stethoscope disinfection(1).

The most common disinfectant used by doctors (60.1%) was alcohol swab (Ethyl alcohol) in our study. Similarly, studies by Pal K et al and Sahb et al witnessed that the doctors frequently use Ethyl-alcohol based agents for sterilizing stethoscopes(10, 15). The majority of medical students (83.5%) in our study considered alcohol swabs as the best disinfectant for stethoscopes. While on the other hand Pal K et al unveiled that more than 50% of medical students had no idea regarding the use of alcohol based agents(15). This result indicated that the knowledge regarding appropriate stethoscope disinfectant is good among medical students of our study population.

Quite a few respondents (35.7%) alleged that they don't know how to clean their stethoscopes. This raises a concern and requires work to educate doctors and medical students as to how to clean stethoscopes properly. An overwhelming number of participants (94.9%) said that they were not provided with any material to disinfect their stethoscopes; this might be one of the reasons for a very low number of doctors and students disinfecting their stethoscope frequently. Authorities should look into this matter and provide proper disinfectants so that practice of stethoscope disinfection could be enhanced and nosocomial infections could be reduced.

Conclusion

Our study concluded that there is a lack of practice by medical providers to disinfect their stethoscope in spite of considering stethoscope as a potential vector for nosocomial infection. Therefore, measures should be taken to elevate the practice of stethoscope disinfection to reduce the nosocomial infections effectively.

Conflict of interest:
The authors of the study did not have any type of conflict of interest with any person, body or institute.

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World Perspective of Divorce in Selected Countries: A Sociological Appraisal

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Abstract

The present paper investigates the quality and quantity of divorce events taking place all over the world more than any time before. The given action creates social, economic, educational, emotional and many more consequences for the families of various cultures, religions, social settings, moralities, and administrative infrastructures. While divorce is a stigma in one society, it is a regular norm in the other. So, attitudes toward divorce is quite different in the societies of the world. Divorce is being facilitated all over the world due to modernization and industrialization processes, and the outcome of social change. Sociologists must be quite vigilant to the phenomenon which is breaking families and creating social problems of all sorts. However, it is sociology that can judge and assess the demerits of divorce. Many of the apparent social issues emerging such as drug abuse, child labor, criminal behaviors and many more, are somehow or other associated with divorce. Method of research used in the present article is of qualitative type, and the article eventually concludes that the outcome of divorce is widely different in sociological terms affecting both parties of parents as well as children to a greater extent.

Key words: Divorce. Culture. Modernization. Stigma. Social issues

Introduction

Divorce being a painful event for families and societies, is increasingly taking place in almost all societies. It is the beginning of new relationships; both parties (men and women) will encounter new life, new values, and new lifestyles. Though some challenges fade away, new challenges emerge. In post-divorce era, children highly face problems materially, emotionally, and from the viewpoints of caring, socialization etc. Among the industrial countries, USA has the highest frequency of divorce; one of every two marriages leads to divorce. Then it is the European countries having an average of 40% of marriages breaking down into divorce. Due to increasing socio-cultural change that is constantly appearing, in many countries where divorce was a taboo before, it is currently highly taking place. Many non-industrial countries in which women have gained more rights, benefits, education and independence in recent decades, divorce takes place in an unprecedented number, and that becomes a new value, being followed by younger generations. Countries like India and Iran in which a low number of divorces once took place, currently high numbers of divorces are registered every year.

Children's adjustment to divorce in family is quite hard to believe. They are the only members of the family who lose a lot. Parents may remarry and continue life, but children lose the process of socialization, emotional attachments, face loneliness, living with one parent, in a stepfather/mother situation or none (in a nursing home). Such children will eventually repeat the cycle in their twenties or so. Many of such children become child laborers in nonindustrial countries. They are usually called "Parasites" by other members of the society. Children may also suppress emotions and the need for connection with others as a means of self-protection. However, they may rationalize that if they get too close to people, others cannot hurt them. Children may also bully other children due to not having learnt how to express emotions in a right way.

Method of Research

Methodology used in the present article is of qualitative type. In that, various paradigms have been used to find out facts regarding divorce. Qualitative research usually studies people or areas in their natural settings. In finding facts for the research, the researcher engaged in careful data collection and thoughtful analysis of what was relevant. In the documentary research applied in the present article, printed and written materials were widely regarded. The research was performed as a qualitative library type in which the researcher had to refer to relevant and related sources. In the current research various documents were thoroughly investigated, and the needful inferences were made. The data fed by the investigator in the present article is hopefully reliable. Though literature on divorce is very limited, yet the author tried to investigate many different resources in order to elicit the necessary information to build up the text.

Healthy Adjustment

When divorce is taking place, healthy relationships are highly recommended. In that, parents are advised to share their emotional experiences toward their children. In this process, one way is through the practice of emotional coaching (Gottman, 1997). It encourages the divorcing parents to help their children to learn how to process emotions effectively and to regulate strong emotional experiences. Skills that are particularly important in co-parenting, include the practice of principles which better enable parents to regulate their emotions as well.

Active availability of parental and other caregivers is critical after divorce. That is because children generally develop attachment bonds with many significant caregivers including grandparents and other close family friends. But, none is as strong as parents. Children's ability and resilience to changes after the hard process of divorce depends on maintenance of healthy attachment bonds.

Another issue appearing in some families and within some spouses is abandonment or desertion in which sometimes one spouse leaves family, and in that a lot of problems are created for the other spouse and children such as emotional and financial difficulties created as a result. It occasionally happens through migration. It used to occur in fewer instances before, but in recent decades it is appearing more ___ leaving behind lots of family, financial and emotional problems. That is even worse than divorce, since the relationships are not yet officially disrupted; the family is still waiting for the absentee to return. In the US, many such cases are heard especially among the migrants. So, if the disengagement persists, it eventually leads to divorce. However, abandonment has also an impact on the larger society, when society becomes burdened with the responsibility to support the abandoned spouse or family financially through government –funded programs, but the emotional vacuum is still there and un-responded (Durkee, 2010).

Divorce in China

In China both parties of husband and wife can have the power to divorce. But, it requires the agreement of both. At the same time, they should have the economic power to protect themselves such as their property (Retrieved, 2002). Since 1949, after the People's Republic was declared, the country's new Marriage Law was explicitly modified; and the new lawful divorces came into being. Based on that, women had permission to divorce their husbands, and many did so. But the declaration created lots of challenges and many women who were blocked to do so, committed suicide. It has by now become very commonplace--reaching 1.4 for every 1000 people, roughly about twice as compared with the data of 1982. Yet, the divorce rate is less than half of what it is in the United States (Retrieved, 2009). Such a divorce perspective in China is mainly due to social change as a result of economic growth, industrialization and urbanization in that country. Similarly, as more and more women have access to higher education and economic independence, all have contributed to the increasing divorce rate in China.

Moreover, another reason for appearance of more divorces in China is because of an amendment added to Marriage Law in 2001, which shortened the divorce application procedure (Romantic Materialism, 2011). As investigated, high cell phone penetration in China has also destroyed the family harmony and fidelity paving the route to more divorces (Zhang, 2018). As marriage maintenance has decreased due to rising divorces in recent years, many public discussions and governmental organisations often criticize it. To prevent the increasing rare of divorce, some divorce buffer bureaus have been established in some marriage registration offices in certain provinces in order to control some divorce events (Sina.Com 2011). Despite the increasing rate of divorce in China at present, there was a custom sororate marriage there in which a man could marry the sister(s) of his wife, being alive, dead or infertile.

Table 1: Global Divorce Rates (1960-2017)

Year	Percent
1960	12%
1970	16%
1980	26%
1990	28%
2000	35%
2010	41%
2017	44%

Source: BCCL 2000.

Divorce in India

Though divorce was in quite small numbers, and a taboo in Indiaonce, based on social change, higher literacy, industrialization, urbanization and women's higher employment rate, the divorce rate has considerably gone up within all communities in India in recent decades. So, many couples facing difficulties are increasingly deciding to part their ways legally unparalleled with the past in Indian history. But, before the legal divorce takes place, the husband and wife would have lived separately for a year. They should also prove that their marriage has totally collapsed, and needs to be dissolved.

Under such circumstances they can file their petition for divorce.

The Hindu Marriage Act 1955 includes all the citizens of India including Muslims, Christians, Parsis and Jews by region. Divorce law in India highly stresses on adultery. Any one of the spouses indulged in such an act is subject to divorce. Also, in case a wife is acknowledged of any marriage by her husband, can apply for a petition to divorce. Cities like Delhi, Mumbai, Bangalore and Pune are facing increasing numbers of divorces annually. Sociologically speaking, what the country needs in this regard, is more marriage counselors to patch up the differences, and pass away the divorce decisions, and instead, bring about mutual consent between the couples. Divorce, as an unexpected milestone in a person's life in India leads to increasing difficulties. The post-divorce life is challenging in India, being faced by financial hardships especially for the women. Divorces may also be deviated by choosing the wrong and faulty route according to Indian norms and values.

Divorce in the Philippines

The Philippines with a population of over 108 million, does not practice divorce, but the move toward legalizing it is under way. Many couples like other countries have differences with each other, but being Roman Catholic, they cannot apply for divorce. Only Muslims who are roughly 5% of the entire population in that country can do so. The only other country where divorce remains illegal is the Vatican City. A bill passed by the Philippines House of Representatives is giving hope to proponents of divorce. It will hopefully permit and legalize divorce in cases of irreconcilable differences, abuse, abandonment and infidelity.

In case of prohibition of divorce and shortage of population control in the Philippines, the situation has left the country with a total fertility rate (TFR) of 2.7 children for a woman in 2019. As over 80% of people in the Philippines are Catholic, the church has a powerful influence in the country. Under such circumstances many marriages are remaining irreparable in the country. In this way, they want to revive the sanctity of the marriage and family within thepopulation.

Divorce in Germany

While Germany faced the highest rate of divorce among the EU countries in the past, the proportion of divorce has decreased in that country in the past few years. In 2011, a total of 187,640 marriages were dissolved, compared with 148,066 in the year 2018; a decrease of around 21%. Based on the Eurostat, the divorce rate in Germany which is the highest in Europe, or so to say, 2.3 per 1000 people has fallen to 1.9 per 1000 inhabitants; below the average of 2.0 in Europe. Such statistics mean that marriages currently appear to last longer as compared with past decades (Schlun & Elseven, 2020).

The decision to divorce is often a hard one. It is psychologically a difficult time to start and end it. Lawyers play an important role to make it smooth and possible. After divorce has taken place, their child (ren) is/are separated to one of them. However, the child has the right to contact both parents. In order to have a legal divorce, both spouses should have lived apart at least for a year. Similarly, in case both parties are wealthy and have a lot of assets, there would emerge disputes lengthening the process of divorce event. The cost of getting a divorce in Germany depending on circumstance would be between Euro 1000 and 3000. This cost usually has to be split between the couple. However, in case of low income families, the divorce costs could be reduced or totally waived by the court.

Divorce in Australia

In Australia, divorce is not so fast or instantaneous. To apply for a divorce, spouses must be separated for at least twelve months, only then can the divorce procedure start. Lawyers can help in seeking legal advice for divorce.

Support for children under the age of 18 needs to be decided. Similarly, the filing fee for divorce application of $ 910 needs to be paid by the applicants. In case of financial hardships, reduced fees may be applied. However, property distribution or arrangements for children, financial support and other wealth issues are determined later and after the divorce. Marriages that happened overseas may be applicable to divorce under certain conditions such as being Australian citizen, ordinarily living in Australia, and having done the 12 months of separation etc.

Crude divorce rate dropped from 4.6 divorces earlier to just 2 in 2017. One reason for such a drop in divorce rate is a decrease in marriage rate, and more interest in cohabitation. However, as the average life span has increased to 82 in 2016, average age of marriage age has also gone up to 30 years. Divorce rate has increased by 5.2% from 2016 to 2017. In 2017, the number of marriages was 112,954, and the number of divorces was 40,032. So the ratio of divorce to marriage was

$$\text{Divorce to Marriage Ratio} = \frac{\text{Number of Divorces}}{\text{Number of Marriages}} \times 100$$

Table 2: Selected Divorce Rates by Country and Population 2019

Country	Number of Divorces Per 1000 Population	Population 2019
Guatemala	0.4	17.581.742
Qatar	0.4	2.832.067
Peru	0.5	32.510.453
Ireland	0.6	4.882.495
Malta	0.8	440.372
Greece	1.0	10.473.455
Uzbekistan	1.0	32.981.716
Mexico	1.1	127.575.529
Armenia	1.2	2.957.731
Azerbaijan	1.3	10.047.718
Bulgaria	1.5	7.000.119
Italy	1.6	60.550.075
Turkey	1.6	83.429.615
Belgium	2.0	11.539.328
South Korea	2.1	51.225.308
Spain	2.1	46.736.776
Iran	2.3	82.913.906
Czech Republic	2.4	10.689.209
Sweden	2.4	10.036.379
Finland	2.5	5.532.156
United States	2.5	329.064.917
Cuba	2.9	11.333.483
Ukraine	3.1	43.993.638
Russia	4.7	145.872.256

Source: Marriage and Divorce, 2020, American Psychological Association

Also, the most common age for getting a divorce is 45.5 for males and 42.9 for females in Australia.

Divorce in Africa

Widowhood and divorce are very common in Africa. Statistics show that 10% of African women are widows, and out of every six women, one is a divorcee. So, female-headed household are growing all across the continent. Women must seriously struggle to respond to the economic hardship. There is a sort of inequality after divorce in terms of arrangements of child custody, property rights, and inheritance. Women are seriously hurt under the divorce event, and such impacts are really understudied in Africa.

One of the African countries where divorce takes quite a long time is South Africa where there are civil marriages and customary marriage. In both cases, marriage needs to be dissolved by a court. However, in case a spouse is not wanting divorce, divorce could be granted without his or her consent. Legal separation does not exist in South Africa even if you are no longer living with your husband and not divorced. According to law you are still married. There are two types of in South Africa: contested and uncontested divorces. The uncontested divorce is found to be very effective for all the parties concerned. It could be finalized within four weeks, whereas in case of contesteddivorce , it will take more than two years. (Retrieved, 2017).

Niger also in West Africa have divorce courts taking place on sidewalks around which lots of men and women gather to see what is going on. In this way, divorce easily takes place in Niger. In Niger where there is child marriage, abortion is also legal there (New York Times, January 11, 2019).

Eventuality of Divorce

The consequence of divorce is not generally a happy life in any society; in the industrial or unindustrial world. Over 40% of American children experience parental divorce or separation in their childhood (Sun, 2008), which is very hurting and painful. They have to live with a step mother, or step father, or spend their childhood in a home which is not quite natural, and not as warm as their parents' home. They are usually deprived of natural parenting and affection. Such children of divorce are usually deprived of educational attainment, job prestige and good income in their adulthood. Similarly, their psychological well-being is hurt and affected. The situation is a lot different for post-divorce children. They mostly become child labor, and gradually face socio-demographic challenges like early marriage, more children, more mortality, shorter life expectancy and many more.

It has been shown that those who had divorced, did not have a happier life than those who had stayed together (Waite, 2003). Studies show that children after the death

of a parent are usually as happy as before that, whereas children after divorce do not have that level of happiness as before the event (Tebeka, 2016).

Divorce in OECD Countries

Most of the OECD countries have experienced a dramatic change in their divorce rates in the past 50 years; from 1.0 to 1.9 per 1000 population (Aassve, 2007). This unprecedented change in the statistics of divorce is more due to change in social norms and culture to trivialize divorce. World-wide speaking, marriages happening today, are more likely to divorce than generations before because of greater social acceptance and easier procedures of divorce.

In general, standards of living decrease more for the women than for men (Bonnet, et al. 2015). When a woman has the custody of the children, it is even worse. In this way, women are highly more prone to poverty after divorce than what happens to men. Similarly, divorce causes the unemployability of women already employed as they have to care for their children, and poverty of children as well.

However, divorce which is happening more than any time before, has lots of social costs, emotional costs, challenges and poverty for the women and children. So, it is a multi-dimensional risk impacting the well-being of women and resulting in a shorter life span for them.

Asia too as the largest continent has variously been facing rising rates of divorce in its different parts in the past four decades. In East Asian countries, divorce rates have been highly rising since 1980. In Japan, South Korea and Hong Kong, the increase has been considerable since 1990. As a special case, between 1995-2008 when the financial crisis happened, substantial increase in divorce emerged there. For example, family honor, appearances, and number of children were points impacting the rise in divorce in South Korea. Likewise, the big city environment and increasing economic independence of women affected the divorce rate to rise. Asia with a high degree of urbanization, is widely facing change through divorce (Premchand, 2017).

Conclusion

Divorce leads to a large number of problems for the separated partners, children, parents of the divorced etc. Results of divorce are different from country to country according to socio-cultural norms and values of those countries. Children will be the most affected after divorce. They are seriously emotionally affected, and will likely not be able to use their potentialities. A cycle of repeated divorces may follow in the years to come too. Adjustment will be hard for the children to pursue. Similarly, availability of parental care-giving would deteriorate, and the substitutes like grandparents cannot provide the same standards as the parents. Another type of marital suspension which happens and is different from legal and formal divorce, is abandonment or desertion in which usually the male spouse leaves home without saying where he is. Such an action too seriously hurts the family.

After divorce, women lose more. They may age without marrying again. Divorce being a stigma, in many countries and cultures, leaves women with hardships. They will be socially and economically in trouble. The proportion of divorce has gone up in different countries since 1950 according to their social and industrial change. Women's economic independence has highly impacted the rate of divorce in any country whether industrial or industrializing. Countries where which divorce was entirely a taboo, is currently happening normally there more due to social change and urbanization in the country. Tables show how divorce is growing in traditional and modern societies. Some countries like the Philippines with special moral and religious code of behavior does not allow the divorce practice, but is intending to enact new laws to legalize it. The divorce rate is quite high in countries like US and Germany, a practice appearing as a social norm. In traditional societies illegitimacy is something forbidden (a social stigma), while in the modern world it is widely observed and practiced. In the industrial world, divorce occurs more in later ages, while in the developing world it mostly happens in earlier ages. However, divorce needs more interpretation and analysis in sociological and psychological terms in order to reduce it. One main reason contributing to the increase of divorce worldwide, is the application of cell phones that emotionally part spouses from each other.

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Parkinson's Disease: An update on Pathophysiology, Epidemiology, Diagnosis and Management. Part 2 : Etiology and Pathophysiology

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Abstract

Parkinson's disease is a common neurodegenerative disorder which involves the loss of nigral dopaminergic neurons in particular. The attributes of the cardinal motor are rigidity, bradykinesis, tremor in rest and postural instability. Nonmotor symptoms are normal in the course of the disease both early and late, and include autonomic, neuropsychiatric and cognitive disorders. Parkinson's disease has symptoms beyond the nigrostriatal system so it is not shocking that some motor characteristics (such as postural instability) and many non-motor characteristics have a restricted response to dopaminergic medications. The cause is uncertain but there is growing evidence that this could be due to a combination of ecological and hereditary factors. Treatment intends to control the patient's manifestations by renewing the dopaminergic framework with levodopa or dopamine agonists. Treatment during the early stage of Parkinson's disease has developed, and studies recommend that dopamine agonist monotherapy may forestall the response fluctuations that are associated with progression of the disease. However, L-dopa therapy remains the most effective treatment available. In the advanced stage, therapy focuses on improving the management of a variety of different health conditions. Successful control of motor activity variability (e.g. "wearing off," on-off variations, deterioration at night, early morning deterioration and dyskinesias) and psychological issues is frequently conceivable with explicit treatment approaches. Surgical treatment is a possibility for a well-defined patient category. The latest update of Parkinson's disease will be reviewed fully in eight review papers.

Key words: Parkinson, Etiology, pathophysiology, Genetic, Environment

Pathophysiology

Parkinson's disease is a neurodegenerative condition involving several neural pathways of the motor and the non-motor. It happens when all nerve cells in the brain area of the substantia nigra (i.e., "black substance") die or get damaged and degenerate (Aminoff, 2007). Such neurons usually produce dopamine, a chemical messenger responsible for transmitting signals between the substantia nigra in the basal ganglia and the next brain "relay station," the corpus striatum, to create smooth, deliberate muscle action. Loss of dopamine causes striatum nerve cells to fire out of control, leaving patients unable to normally guide or regulate their movements. Typically for many years after the start of neurodegeneration, the first signs of PD will not occur because there is plenty of dopamine left in storage to compensate for the diminishing supply. An individual will lose in any event half of the dopamine in their cerebrum before seeing that something isn't right with their body. In patients with PD, the substantia nigra can lose 60 per cent to 80 per cent or more of dopamine-producing cells. It is not clear what caused this cell death or disability (Hauser, 2006). (Figure 1)

There are no common, accepted criteria for Parkinson's disease neuropathological diagnosis, as the specificity and sensitivity of its characteristic findings have not been clearly defined. However, the following are the 2 main neuropathological findings in Parkinson's disease:

• Loss of substantia nigra pars compacta pigmented dopaminergic neurons
• The development of Lewy bodies and Lewy neurites (Figure 2).

The loss of dopamine neurons occurs most commonly in the lateral substantia nigra ventrals. Approximately 60-80 per cent of dopaminergic neurons are destroyed before the Parkinson disease motor symptoms appear.

Many people who at the time of their death were considered to be neurologically fine are found to have Lewy bodies (LB) on autopsy examination. Hypothesized to reflect the presymptomatic process of Parkinson's disease were these accidental Lewy bodies. With age the incidence of incidental Lewy bodies is growing. Note that Parkinson's disease is not unique to Lewy bodies, although they are present in some cases of atypical parkinsonism, Hallervorden-Spatz disease, and other disorders. These are nevertheless a hallmark result in Parkinson's disease pathology.

Parkinson's disease is depicted by two main pathological processes:

(a) premature preferential loss of dopamine neurons;
(b) accumulation of α-synuclein-composed Lewy bodies, which are misfolded and accumulate in various systems of Parkinson's disease patients; what cycle occurs first, is unclear.

LBs are intraneuronal, small, eosinophilic inclusions composed of more than 90 proteins with a hyaline core and a light peripheral halo; their main components are-Synuclein and ubiquitin (Spillantini et al, 1997). The ability of α-synuclein to misfold, become insoluble, and form b-sheet-rich amyloid aggregates that accumulate, form intracellular inclusions. The intermediates in this aggregation cycle are the toxic oligomeric and proto-fibrillary types that disrupt mitochondrial function (Hsu et al., 2000), lysosomal and proteasomal function (Snyder et al., 2003), damage biological membranes (Danzer et al, 2007) and cytoskeletons (Alim et al., 2004), alter synaptic function (Scott et al., 2010) and trigger neuronal degeration.

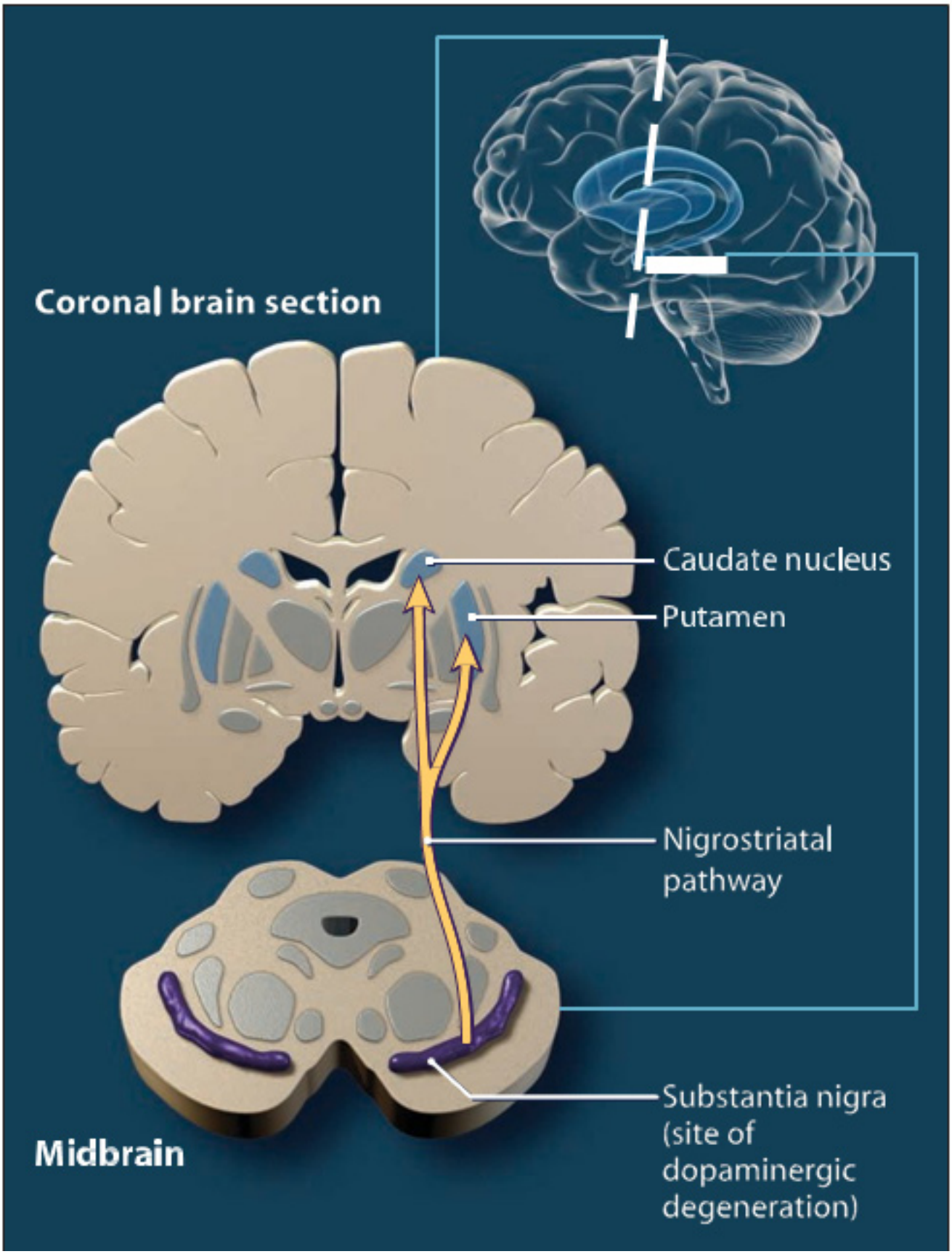
A sequential model of LB development and α-synuclein deposition, starting with the dorsal motor nucleus of the glossopharyngeal and vagal nerves and anterior olfactory nucleus, eventually spreading to the brain stem and later to the mesocortex and allocortex and finally to the neocortex, was suggested (Braak et al., 2003) (Figure 1). α-Synuclein continues to propagate through the neurons in a prion-like fashion and this propagation mechanism is likely to underlie the development of previously reported pathological alterations (Brundin et al. 2016). In addition, some data indicate that α-synuclein aggregation can start and spread rostrally in the autonomic plexi of the gut (Klingelhoefer & Reichmann, 2015) and can be influenced by the gut microbiome (Sampson et al., 2016).

There is a progressive degeneration of neurons over several years based on clinical research (Braak et al. 2003), with each affected site leading to a different symptomatology of Parkinson disease (Table 1). As motor symptoms are apparent, the substantia nigra on pathological inspection shows a 30–70 percent cell loss (Jankovic, 2005). PD's non-motor symptoms stem from the loss of neurons in areas of the brain outside the substantia nigra and include chemicals other than dopamine, particularly acetylcholine. Cognitive dysfunction, mood disturbances and impulse regulation disturbances are associated with dopamine deficiencies outside the basal ganglia, or in serotonergic and noradrenergic systems (Kim et al, 2015, Hemmerle e al., 2012). Autonomic dysfunction was associated with pathologies outside the brain including the spinal cord and the autonomic peripheral nervous system (Kieburtz & Wunderle 2013).

Etiology: Environmental and Genetic Factors

The precise cause of Parkinson's disease is unclear, although a combination of environmental factors superimposed on genetic predisposition or vulnerability is thought to result (Table 2). (Racette & Willis, 2013, Kieburtz & Wunderle, 2015, Covy & Giasson, 2011). There is growing proof that genetic and environmental insults that lead to Parkinson's disease commonly lead to abnormal forms of a normal protein, α–synuclein, that appears to contribute to cell death (Luk & Lee, 2014). Parkinson's onset can be graded as adolescent (age < 21 years), early onset (21–50 years), and late onset (generally > 60 years). The juvenile

Figure 1: Coronal section of the brain, showing nigrostriatal pathways and location of selective dopaminergic degeneration in patients with Parkinson's disease.



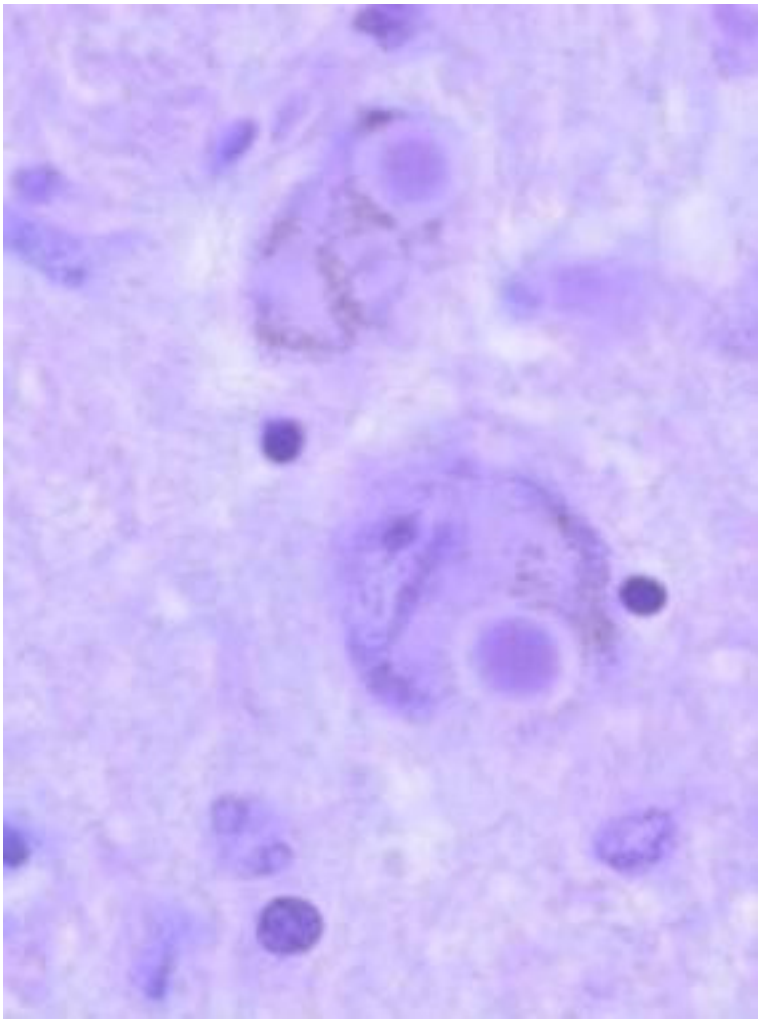


Figure 2: Lewy bodies are intracytoplasmic eosinophilic inclusions, often with halos, that are easily seen in pigmented neurons, as shown in this histologic slide. They contain polymerized alpha-synuclein; therefore, Parkinson disease is a synucleinopathy.

Table 1: Braak staging of Lewy body deposition[10]

Stage	Sites affected by Lewy bodies	Major symptoms
I	Dorsal motor nucleus of the vagus nerve & olfactory tract	Constipation, anosmia
II	Locus coeruleus and subcoeruleus complex	Sleep and mood dysfunction
III	Substantia nigra	Motor symptoms of Parkinson
IV–VI	Cortical involvement	Dementia, psychosis

type is uncommon, is frequently hereditary (in as many as 50 percent of cases), is most commonly associated with a mutation of the parkin gene and has an atypical appearance. (Ferguson and others, 2016). For Parkinson's disease patients, 10 percent -16 percent have a first- or second-degree relative affected; first-degree relatives may have twice the chance for Parkinson's disease compared to the general population. The occurrence of a healthy family history is not significantly significant for early- and late-onset Parkinson's disease (Ferguson et al, 2016).

While the cause of Parkinson's disease is still unclear, it is generally accepted that most idiopathic disease cases are triggered by environmental and genetic factors interacting.

Oxidation Hypothesis

While PD pathogenesis is unclear, one mechanism of substantia nigra toxicity that may play a role is the production of cellular damage from oxyradicals (Alam, 1997). Dopamine creates free radicals from auto-oxidation and the metabolism of monoamine oxidase (MAO). Typically, there are many anti-oxidant mechanisms inside and outside the neurons to minimize any damage that may be evoked by an attack by free radicals, but such defense in PD can be overcome or impaired. Often known as the etiological mechanism of PD (LeWitt, 2000) are excitotoxicity, programmed initiation of cell death, and chronic infection.

The oxidation hypothesis indicates that free radical damage resulting from the oxidative metabolism of dopamine plays a role in Parkinson's disease development or progression. MAO's oxidant metabolism of dopamine contributes to hydrogen peroxide formation. Normally, glutathione cleans hydrogen peroxide easily, but if hydrogen peroxide is not sufficiently cleansed, it can lead to the formation of highly reactive hydroxyl radicals that can react with lipid membrane lipids to cause lipid peroxidation and cell harm. The levels of reduced glutathione in Parkinson's disease are decreased, indicating a lack of protection against free radical development. In substantia nigra, iron is increased and can serve as a source of donor electrons, thereby facilitating the creation of free radicals.

Parkinson's disease is associated with increased dopamine production, decreased protective mechanisms (glutathione), increased iron (a molecule of pro-oxidation), and increased lipid peroxidation proof. This hypothesis raises concern that increased dopamine turnover due to administration of levodopa could increase oxidative damage and accelerate dopamine neuron loss. There's no convincing evidence, though, that levodopa accelerates the progression of disease.

Environmental Factors

Several scientists have proposed that PD happens when either an external toxin or an internal toxin selectively kills dopaminergic neurons (Leegwater & Waters 2008). Environmental risk factors generally associated with the development of Parkinson's disease include pesticide use, rural living, well water use, herbicide exposure and close proximity to industrial plants or quarries (Wirdefeldt, 2011).

An environmental risk factor, such as pesticide exposure or food supply toxin, is an example of an external trigger which could cause PD. The hypothesis is based on the fact that such chemicals, such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and neuroleptic medications, cause parkinsonic symptoms in humans. Nevertheless, no study has yet provided definitive proof that the cause of the disease is a toxin.

Many individuals were identified who developed tetrahydropyridine (MPTP) parkinsonism after self-injection of 1-methyl-4-phenyl-1,2,3,6-. These patients developed bradykinesia, stiffness and tremor which progressed over several weeks and improved with replacement therapy with dopamine. MPTP crosses the blood-brain barrier and is oxidized by monoamine oxidase (MAO)-B to 1- methyl-4-phenylpyridinium (MPP+). (Ballard et al., 1985). MPP+ accumulates in mitochondria and interferes with the function of complex I of the respiratory chain. A chemical resemblance between MPTP and certain herbicides and pesticides indicated that an MPTP-like environmental toxin may be a cause of Parkinson's disease but no particular agent has been confirmed. Nonetheless, the function of mitochondrial complex I in Parkinson's disease is decreased, indicating a common pathway with parkinsonism induced by MPTP.

A meta-analysis of 89 studies, including 6 prospective and 83 case-control studies, found that exposure to pesticides could increase the risk of PD by as much as 80 per cent. (Anderson, 2013, Pezzoli & Cereda , 2103). Particularly toxic is exposure to weed killer paraquat or fungicide maneuvering or mancozeb, increasing the risk of PD by about 2 times. Some of the agents researched in the United States and Europe are no longer used; however, others are still used in developing parts of the world (Anderson, 2013, Pezzoli & Cereda , 2103).

In case-control studies, PD was associated with exposure to any type of pesticide, herbicide, insecticide, and solvent, with risks ranging from 33% to 80%. (Anderson, 2013, Pezzoli & Cereda , 2103). Increased PD risk was also associated with proxy conditions of exposure to organic pollutants such as agriculture, well-water drinking, and rural life. Additionally, the risk appeared to increase with the exposure length. (Anderson, 2013, Pezzoli & Cereda, 2103).

As well as a meta-analysis of prospective research, the National Institutes of Health-AARP Diet and Health Survey found that higher consumption of caffeine was correlated with lower risk for Parkinson's disease in both men and women. A similar association for smoking and risk of Parkinson's disease has been found.[Liu et al, 2012). The biological mechanisms underlying the inverse relationship between the risk of caffeine or smoking and Parkinson's disease are not well elucidated.

Genetic Factors

Parkinson's disease is usually intermittent, and the disorder has no family history. A variety of genetic variants of the disease have been identified recently, and studies into these unusual inherited types may help to explain this condition's pathophysiology. Eight genetic loci have been identified for monogenic manifestations of Parkinson's disease, or dopa-responsive parkinsonism (Table 3). (Gasser, 2001, Valente and others, 2002, Van Duijin et al., 2001).

In the pedigrees of autosomal dominant Parkinson's disease, in several Greek and Italian families and in a German family, 2 missense mutations in the α-synuclein gene (PARK1) have been identified. Although the 2 mutations tend to be a rare cause of the disease, α-synuclein has gained a great deal of attention because it is one of the Lewy bodies' main constituents. A large range of mutations in the parkin gene (PARK2) were observed in pedigrees of autosomal recessive early onset parkinsonism in around 50 per cent of families in which at least one of the affected siblings exhibited symptoms at or before age 45. A broad twin study revealed that genetic factors play a major role in pathogenesis of Parkinson's early onset disease but not Parkinson's late-onset disease (diagnosed after age 50) (Tanner et al., 1999).

LRRK2 is the first gene often mutated to late-onset autosomal-dominant PD (Di Fonzo et al., 2006). Many distinct mutations have been associated with genetic causes. Recently, nine mutations involving a novel gene, leucine-rich repeat kinase 2 (LRRK2), were identified as the cause of autosomal-dominant PD in parentages, and some of them were previously related to the PARK8 locus on chromosome 12. LRRK2 mutations are hereditary and sporadic PD fairly normal genetic causes.

Those mutations were also found in different populations. LRRK2-associated PD's clinical and pathological characteristics are distinct from those of idiopathic PD; however, there is significant clinical and pathological variation even among parents (Whaley et al., 2006).

Recently, mutations in the LRRK2 gene encoding have been linked to autosomal-dominant parkinsonism, clinically indistinguishable from normal, idiopathic, late-onset PD. Thus the LRRK2 protein has emerged as a potential therapeutic treatment option. LRRK2 is large and complex, with numerous enzymatic and protein interaction domains, each targeting pathogenic mutations in fam ilies with Parkinson disease.

A genome-wide search for idiopathic Parkinson's disease (DeStefano et al., 2001) found no clear evidence for association. Another late-onset Parkinson's disease genomic test (onset 40–90 years) however indicated several genetic influences (Scott et al., 2001). A recent heritage research in Iceland indicated a major genetic link to the development of Parkinson's late-onset disease (onset after 50 years) in the population, and a locus of susceptibility to Parkinson's disease in Icelandic patients was identified (Sveinbjornsdottir et al., 2000, Hicks et al., 2002).

Melanoma

Speculation has been rife over a relationship between PD and melanoma for years. It was originally theorized that the medication levodopa contributed to an increased risk of skin cancer but this was not supported by research. However, subsequent trials in patients with PD have since found an increased risk of melanoma. One specific 2017 study found that Parkinson's patients had around a 4-fold increased risk of pre-existing melanoma(Dalvin et al., 2017). Another study found the risk to be 7-fold (Constantinescu et al., 2014).

Mechanisms of disease and genetics

The reason for PD degeneration of the nerve cells has not been established. Genetics can be a tiny part of this. Studies of toxic PD models and genes involved in hereditary manifestations of PD suggest two main pathogenetic mechanisms: (1) protein misfolding and aggregation, and (2) mitochondrial dysfunction contributing to oxidative stress (Leegwater, 2008).

SNCA, the gene encoding for α-synuclein, was the first gene linked to PD, and A53 T was the first pathogenic SNCA mutation found (Polymeropoulos et al., 1997). This mutation, like other pathogenic mutations, gives α-synuclein a greater tendency to misfold and accumulate than the wild-type mutation; other pathogenic SNCA mutations affect the amount of synuclein (either through duplications or triplications, either altering its expression or its clearance), and alter its post-transcriptional modifications, and/or its interaction with other cellular organelles and transport systems. In addition, existing evidence has highlighted the function of α-synuclein in triggering immunological response, and it has been shown that activated microglial cells directly engulf α-synuclein in an effort to clear it up (Rocha et al., 2018). Interestingly, upregulation of α-synuclein expression has also been observed in idiopathic PD patients (Chiba-Falek et al.,).

Several genes found in familial PD (α-synuclein, parkin, and ubiquitin carboxy-terminal hydroxylase L1) encode for proteins involved in the ubiquitin – proteosome system, which is responsible for normal protein degradation and clearance within eukaryotic cells. Mutations in these genes appear to be related to mishandling and protein aggregation, which in turn results in cell death (Leegwater-Kim, 2008).

Another essential disease mechanism is dysfunction of the mitochondrial function (Schapira et al., 1989). In family types of PD specific genes control mitochondrial functions. PINK1 (Valente et al., 2004) and Parkin (Kitada et al., 1998) interact in a quality control pathway for mitochondria: PINK1 is a serine/threonine kinase that 'tags' damaged mitochondria and activates the mitophagy pathway by recruiting Parkin, an E3 ubiquitin ligase. DJ-1 (Bonifati et al., 2003) plays a key role in controlling calcium flux in the mitochondrion, shielding the cell from oxidative stress

Table 3: Summary of genes associated with Parkinson disease (PD)

Gene	Locus name	Protein name	Chromosome	Inheritance	Clinics	Frequency in PD	Protein function
SNCA	PARK1/4	a-synuclein	4q21–23	AD	EOPD	<1%	Synaptic
PRKN	PARK2	Parkin	6q25–27	AR	EOPD, slow progression, + dystonia	1%–5% (up to 44% in EOPD)	Ubiquitin-ligase
UCHL1	PARK5	UCHL-1	4p14	AD	EOPD, LOPD	<1%	Uncertain
PINK1	PARK6	PTEN-induced putative kinase I	1p35–37	AR	EOPD, slow progression	2%–5%	Mitochondrial kinase
DJ-1	PARK7	Protein DJ-1	1p36	AR	EOPD, slow progression	1%	Cellular sensor of oxidative stress
LRRK2	PARK8	Leucine-rich repeat serine/ threonine-protein kinase 2	12p11–q13	AD	LOPD, slow progression	1%–5% (up to 40% in North African Berber Arab patients)	Multiple functions domain dependent
ATP13A2	PARK9	ATPase type 13A2	1p36	AR	Atypical parkinsonism, Kufor Rakeb syndrome	<1%	Lysosomal protein
PLA2G6	PARK14	A2 phospholipase	22q13	AR	EOPD, dystonia-parkinsonism	<1%	Unknown
FOXB7	PARK15	F-box protein 7	22q12–13	AR	EOPD, atypical parkinsonism	<1%	Unknown
VPS35	PARK17	Vacuolar protein sorting-associated protein 35	16q11	AD or risk	LOPD	<1%	Unknown
GBA					Glucocerebrosidase	1q21	Risk factor
Earlier onset +	dementia	5%–25% (10%–30% in Ashkenazi Jewish patients)	Lysosomal protein				

AD, autosomal dominant; AR, autosomal recessive; EOPD, early onset PD; LOPD, late onset PD.

induced by the dopaminergic neuron and dopamine toxic city's pace-making operation. Within the SNpc of PD brains there are records of mitochondrial DNA abnormalities, probably somatic, (Bender et al., 2006).

The body of evidence links PD to dysfunction in the cell clearance pathways, and PD has been correlated with multiple genes linked to autophagy (Gan-Or et al., 2015). Mutant LRRK2 (Funayama et al., 2002) interferes with autophagy, and alpha-synuclein degradation has been reported to slow, leading to its accumulation (Yue & Yang, 2013). ATP132A mutations establish lysosomal dysfunction (Dehay et al., 2012) and induce parkinsonism (Kufor Rakeb syndrome), whereas its expression is upregulated in idiopathic PD surviving dopaminergic neurons, indicating its neuroprotective effect (Ramirez et al., 2006).

GBA1 mutations, which encode for glucocere-brosidase (GCase), a lysosomal enzyme that metabolizes glucosylceramide and whose defects cause Gaucher disease, constitute the most important genetic risk factor currently identified for PD. GBA1 mutations are highly prevalent in PD patients with an odds ratio of 5.43; GBA1 mutations occur between 5% and 25% of PD patients. GBA's contribution to PD pathogenesis is complex, and PD pathogenesis includes interactions with different pathways: a reciprocal relationship with α -synuclein accumulation, endoplasmic reticulum stress, and mitochondrial dysfunction. GBA-related PD is clinically distinct from sporadic PD, while patients normally experience earlier onset, quicker decline (depending on the mutation) and increased risk of cognitive dysfunction (Balestrino et al., 2018).

Nine rare LRP10 variants have recently been associated with LBs (DLB) in family PD, PD dementia and dementia (Quadri, et al., 2018). LRP10 is a protein that shuts between the trans-Golgi network, plasma membrane and endosomes. Certain proteins involved in this network, including VPS35 and GGA1, were previously linked to PD. More study is required to explain the pathogenetic role of PD and other neurodegenerative disorders with LB pathology alterations in these pathways (Williams, 2017).

Several causative genes have been identified, usually eliciting young-onset parkinsonism. However, identified genetic and familial forms of PD are rare. Mutations in the gene for the protein α-synuclein, located on chromosome 4, result in autosomal-dominant parkinsonism. The function of this protein is not known. The most commonly occurring genetic defect affects the gene for the protein called parkin on chromosome 6 (Kawahara, et al., 2008). Mutations in this gene result in autosomal-recessive parkinsonism, which is slowly progressive with onset before the age of 40.

A relatively new theory looks at the role of genetic factors in PD growth. Around 15% to 20% of patients with PD have a close relative who has had parkinsonian symptoms such as tremor (Nelson et al., 2005, Jankovic et al., 2008).

Several causative genes have been identified, causing typical parkinsonism in the young. However, genetic and family types known for PD are rare. Mutations in the α-synuclein protein gene, located on chromosome 4, result in parkinsonism which is autosomal dominant. The protein's function is not understood. The most common genetic mutation involves the protein gene called parkin on chromosome 6 (22). Mutations in this gene result in autosomal-recessive parkinsonism, which is gradually progressive, starting before the age of 40 years.

Mutations in the parkin gene are the most common cause of parkinsonism in the family, and a growing number of studies indicate that stress factors associated with sporadic PD encourage accumulation of parkin in the insoluble fraction. Accumulation and mutations of parkin and α-synuclein in these genes were associated with familial PD. Accumulation of α-synuclein may contribute to the pathogenesis of PD and other Lewy body diseases by promoting alterations in solubility of parkin and tubulin, which may in effect compromise neural function by damaging the cytoskeleton of the neurons. Such results provide new insights into the possible existence of pathogenic α-synuclein and parkin interactions in PD (Kawahara et al., 2008).

Why SNpc dopaminergic neurons are especially vulnerable to neurodegeneration remains obscure; the autonomous pace-making function of SNpc dopaminergic neurons and calcium homeostasis has been suggested to play a significant role (Cali et al., 2011). As of late, there has been growing interest in the role of the microbiome in pathogenesis of PD and other neurodegenerative diseases. Pathogenetic pathways include dopamine synthesis and metabolism modifications, immune system dysregulation and inflammation, and improvements in enteral mucosal permeability (Spielman et al., 2018).

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Anti-TNF-α drug-induced lupus: A Case Report

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Abstract

Background: It is expected that incidence of anti-TNFα induced lupus (ATIL) will probably increase with more widespread use of anti-tumor necrosis factor-α (anti-TNFα) agents.

Case Report: We report a rare presentation of ATIL with hepatitis for a woman who has Crohn's disease and was treated with infliximab for 9 months. She had clinical and biochemical improvement after discontinuation of infliximab and starting steroid therapy.

Conclusion: Treatment with Infliximab may cause a lupus-like syndrome, which can be reversed upon its discontinuation.

Key words: Drug-induced lupus erythematosus, anti-TNFα, hepatitis, infliximab.

Introduction

Drug-induced lupus erythematosus (DILE) is a syndrome with symptoms, signs and laboratory findings similar to idiopathic systemic lupus erythematous (SLE). Sulfadiazine was the first medication reported to cause drug-induced lupus (1). Since then, more than 80 drugs have been implicated in the onset of DILE (2).

In 1998, the introduction of tumor necrosis factor-α blocking therapies (anti-TNFα) marked the beginning of a new era in the treatment of chronic inflammatory human diseases, including rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS) and Crohn's disease (CD) (3). The relationship between anti-TNFα agents and DILE was confirmed by the disappearance of symptoms after withdrawal of the implicated drugs. Treatment with infliximab and etanercept has been commonly associated with drug-induced lupus erythematous, but it is rarely related to adalimumab (4,5) as infliximab and etanercept have been widely used for relatively longer periods (6).

According to post-marketing studies, anti-TNFα induced lupus (ATIL) has an estimated prevalence of 0.19–0.22% for infliximab, 0.18% for etanercept, and 0.10% for adalimumab. Nevertheless, in randomized controlled trials, the prevalence is higher, reaching 0.78% (7).

We report a Saudi female patient, who developed drug-induced lupus erythematosus after being treated with infliximab for management of refractory Crohn's disease.

Case Report

In September 2019, a 35 -year-old woman presented to the outpatient clinic in McMaster University Hospital, with malaise, body aches and polyarthralgia affecting the ankles, knees, the shoulder, elbows, and wrists.

She was diagnosed with Crohn's disease in 2004, based on consistent symptoms and colonoscopy with biopsies. Colonoscopy showed ulceration in terminal ileum with highly suggestive histology focal crypt irregularity, focal inflammatory infiltration and pyloric metaplasia. She had no past medical history apart from Crohn's disease. She reported a family history of colon cancer in her father at the age of 50 years.

Her prior medications included multiple courses of prednisone (40 mg/day) and azathioprine (150 mg/day). In May 2012, she developed a perianal abscess that was treated with antibiotics with complete response. However, in May 2018, she had recurrent perianal symptoms with perianal fistula drainage that did not respond to antibiotics. She was initiated on infliximab at standard induction and maintenance dose (5 mg/kg every 8 weeks) concurrent with ongoing azathioprine. Unfortunately, she did not respond after her induction doses with infliximab. Therapeutic drug level monitoring was sent at week 6 and was 16 AU/ml. The patient was referred to a colorectal surgeon for further management and consideration of Seton insertion.

On regular blood work conducted to monitor her while on azathioprine, serum ALT was raised to 63 U/L (normal <30 U/L). Therefore, azathioprine was withheld and her serum ALT was normalized.

In May 2019, a follow-up drug trough level of infliximab was 1.6 µg/mL. Subsequently, her infliximab dose was increased to 7 mg/kg every 6 weeks. In September 2019, she developed body aches, joint pains involving most of the small joints of her hands, wrists and large joints of lower limbs including knees and ankles.

Serologic workup revealed elevated titers of antinuclear antibodies (ANA): 1/640 (negative <1/160) and anti-double stranded (ds) DNA: 69 IU/mL (normal <7 IU/mL). Her other serological workup was negative including anti-ENA, anti-Ro, La, Sm, RNP, Scl-70, Jo1, and anti-histone. She also had elevated transaminitis with serum alanine aminotransferase (ALT) 450 U/L, aspartate aminotransferase (AST) 411 U/L, alkaline phosphatase (ALP) 106 U/L, total bilirubin 6 mg/dL, with negative serology for viral hepatitis (Anti-HAV, HBsAg, Anti-HCV).

Infliximab was discontinued and she was started on oral steroid therapy. She responded well and liver enzymes improved afterward. Our followed plan was to watch and see, monitor her liver enzymes and other relevant parameters.

Discussion

Our case presented with Crohn's disease in 2004, and was treated with azathioprine. However, in 2018, she had a recurrent perianal fistula which did not respond to treatment. Therefore, she was initiated on infliximab, after which she developed DILE.

Infliximab is a chimeric monoclonal antibody which targets TNF-α. It is efficacious in treatment of patients with Crohn's disease (8). It has been noted that treatment with infliximab is known to produce an increase of autoantibodies, but not clinical disease (10). However, the serologic workup of our patient showed elevated titers of antinuclear antibodies, associated with symptoms suggestive of SLE, i.e., body and joint pains.

In cases of CD, anti-TNFα agents have been implicated (1). In the first years after the introduction of anti-TNFα, most cases of ATIL were reported in infliximab-treated patients with RA (9-10), PsA or CD (9-11). RA and CD are the two most commonly autoimmune diseases associated with this syndrome, with a 2:1 risk for women compared with men for DILE-like syndrome (12).

Several pathogenic hypotheses have been suggested for ATIL development. Some authors suggest that it results from decreased CD44 expression, which interferes with apoptosis, affects the clearance of apoptotic neutrophils and nuclear debris by phagocytes and promotes autoantibody production against other nuclear antigens and DNA (13-18). Another hypothesis states that immunosuppression by anti-TNF increases infection rates, and in turn activates polyclonal B-lymphocytes and drives autoantibody production. A third hypothesis implies 'cytokine shift' by which anti-TNF alpha suppresses T-helper 1 immune responses and favors T-helper 2 cytokine production, IL-10, and INF-alpha, and promotes humoral autoimmunity (19-23).

Recently, it has been reported that the rate of clearance of dead cells, increased number of plasmacytoid dendritic cells, along with decreased levels of TNFα may influence who will develop autoimmunity and eventually SLE, after treatment with anti-TNFα (24).

ATIL manifestations include malaise, fever, weight loss, polyarthritis, serositis with pleurisy and pericarditis, myositis, hematological (anemia, leukopenia), renal and neurological disorders (10). Cutaneous manifestations like skin rashes are more common in ATIL compared to DILE, whereas myalgias are more common in DILE compared to ATIL (10). The incidence of fever is similar in both diseases. ATIL can occur within months or even years after exposure. Usually full remission of symptoms follows the discontinuation of the inciting drug within weeks (1).

Some authors have suggested there should be a temporal relationship between symptoms and therapy, and at least four American Congress of Rheumatology criteria met for diagnosis of SLE (25). However, most cases do not meet

the full criteria for this diagnosis. The clinical presentations of ATIL associated with adalimumab, etanercept, and infliximab are all similar (7,9, 26).

Case series from the USA reported significant differences between classical DILE and ATIL, with regard to autoantibody profiles (10). Classical DILE was strongly associated with ANA (>99%) and anti-histone antibodies (>95%), while anti-dsDNA antibodies were essentially absent (<1%) (7). In contrast, of the 33 ATIL cases only 57% were anti-histone positive, while 90% were anti-dsDNA positive. Positive ENAs and hypocomplementemia were also more common in ATIL compared with classical DIL in the US study (10).

Currently, there are no diagnostic criteria for ATIL. However, physicians should look for the presence of one or more of the following: (i) temporal relationship between anti-TNFα and symptoms, (ii) at least one serological finding, such as ANA or anti-dsDNA compatible with American College of Rheumatology (ACR) and (iii) one non-serological finding, including arthritis, serositis, hematological disorders, malar rash compatible with ACR. In clinical practice, these findings can be considered for early diagnosis (19).

Our patient met these criteria including arthritis with high ANA, anti-dsDNA. Moreover, she had elevated transaminitis with high serum ALT. We believe that transaminitis is a part of ATIL. However, Shovman et al. (25) noted that ATIL-associated transaminitis is a rare presentation. Only one other case report of ATIL has been reported which was associated with serositis and hepatitis.

After discontinuation of Infliximab, our patient's condition improved. Ramos-Casals et al. (7) stated that discontinuation of the offending drug is usually the first action to be taken for management of DILE. In nearly all cases, this leads to resolution of symptoms. This is usually accompanied by a decrease in the levels of autoantibodies. Some cases may require further management for improving their symptoms, which includes corticosteroids, and immunosuppressive agents, like azathioprine, cyclophosphamide, methotrexate or mycophenolate.

There is limited evidence, in terms of whether patients diagnosed with ATIL can receive an alternative anti-TNFα. One study reported four out of five patients who tolerated alternative agents after discontinuation of infliximab (27).

Conclusion

Patients with Crohn's disease may develop DILE after being treated with infliximab. However, this developed condition can be reversed upon discontinuation of this agent.

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