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This is the last issue this year. The journal this year has moved forward and gained further status in the region and the World. We would like to thank all our readers, authors, the editorial office and the production team for their great effort.

A paper from Saudi Arabia looked at critical appraisal and validity. The authors stressed that many medical schools and residency programs are teaching critical appraisal of articles, by using worksheets. Teaching critical appraisal of validity requires the instructor to use different worksheets for each type of question, which are difficult to remember and require the learner to have the worksheets on hand. RABI is an acronym developed to appraise the validity of therapy, systematic review, and diagnosis and prognosis articles. The items included were derived from user's guide to medical literature, centre of evidence based medicine critical appraisal worksheets, Cochrane risk of bias (ROB) tool and quadas-2 tool. A quantitative evaluation of RABI with the user's guide worksheets in relation to items included and item's sequence. Participants of six three-day evidence based medicine courses were involved in this study. 217 of 243 (89.3%) participants completed the study. There was no statistical difference between RABI and user's guide to medical literature. Participants believe that it is easy to use and remember. The authors concluded that RABI is an acronym, each letter indicates certain items for the four domain questions, which made it easy to remember and use by teachers and learners.

In this issue a paper from Riyadh looked at microalbuminuria as a Risk Factor for Renal Dysfunction in Diabetic Patients in the British and Saudi Arabia Populations. The author stressed that Diabetic Nephropathy is the most common cause of end renal failure worldwide.

Microalbuminuria is considered to be the first risk of Diabetic Nephropathy, which can be prevented and treated at early stage. Antihypertensive drugs have been shown to reduce factor of Microalbuminuria and renal dysfunction.

A paper from Erbil assesses children's knowledge and the impact of specific health awareness program on the weight status of children. Out of 1200 basic education school children, 89 (47 males and 42 females) were identified as overweight and later on involved in a health awareness program using a health education booklet. Three months later, weight of the overweight children was measured again plus that of a number of normal weight children for comparison purposes. The study revealed that health awareness program had no significant weight reduction impact on the total overweight children compared to normal weight children. The authors concluded that multi-level integrated actions need to be taken by schools and the community as a whole emphasizing the importance of controlling the risk factors and managing childhood obesity.

A retrospective, medical records review was conducted in private diabetic clinic in Baghdad on type 2 diabetic patients initiated on Glucovance® tablets between September 2010 and December 2011. Postprandial plasma glucose was measured two hours after lunch meal. Multiple plasma glucose check-up have been taken for each individual, at least three before and three after switching, with the first measure in each case was done after not less than one month from starting the regime, and the mean result for each of them was adopted. Ninety-one patients were enrolled in the current study. At baseline, 78 patients received glibenclamide (85.7%), while the remaining 13 patients (14.3%) were on glimepiride. The mean baseline postprandial plasma glucose in the total population was 317.5 mg/dl. The mean reduction in its level was 91.2 mg/dl ($P < 0.001$) after initiation of Glucovance®. Similar significant individual reduction was seen during subset analysis among those on glibenclamide or glimepiride at baseline. The reduction in postprandial plasma glucose for those on glibenclamide dose within Glucovance® tablets of 2.5. Patients switched from free co-administration of sulfonylurea and metformin to combined combination of glibenclamide and metformin showed marked improvement in postprandial plasma glucose level that was significant regardless the type of sulfonylurea used previously. This improvement was promoted as the total dose of glibenclamide in combination tablets increased.

A paper from Turkey looked at the role of total excision of lymphadenopathies (LAPs) in the treatment of tuberculosis (TB). The authors report on two cases. The first is a 14-year old male presented with weight loss. On physical examination, there were multiple right axillary LAPs with sizes of 3x2 cm. Laboratory evaluation revealed (CRP) 2.1 mg/dL, (ESR) was 73 mm/hr, and Tuberculin skin test showed a 22 mm of induration. The right axillary LAPs were excised, totally, and histological examination demonstrated granulomas with Langhans-type giant histiocytes. After the operation, ESR, CRP, and LDH values and his weight returned to normal without any treatment. The second case is a 43-year old female applied with fever, night sweats, and weight loss. Physical examination, revealed multiple and conglomerated left axillary LAPs with sizes of 6x4 cm. Laboratory evaluation revealed a CRP of 5.2 mg/dL, ESR was 74 mm/hr, and Tuberculin skin test showed a 20 mm of induration. The LAPs were excised, totally, and histological examination demonstrated granulomatous lymphadenitis with epithelioid histiocytes, Langhans-type giant cells, and caseified necrosis. After the operation, fever and night sweats disappeared, and CRP, ESR, and LDH values were normalized. She returned to normal weight within two months without any antituberculous treatment. The authors concluded, that total excision of LAPs if they are limited in number may both have a diagnostic and curative role in TB, probably by decreasing large numbers of bacteria, so remaining small numbers can be eliminated by immune system, alone.

Another paper from Saudi Arabia looked at the role of herbal medicines in cardiovascular diseases. Cardiovascular diseases are one of the major threats to the developing and the developed world. The author aim to assess the effects of various herbal components in preventive cardiology. The search engine used was Pubmed and related websites to explore for chemical constituents, physiological actions and drug interactions through studies and review articles encompassing herbal medicines in cardiovascular diseases. This article presents key features of few commonly used herbs, their modes of action and some interactions with allopathic medications prescribed for cardiovascular disorders. Unfortunately the scientific data on herbal medicine is yet in its infancy and it is of utmost importance to develop more effective, affordable health promotion and treatment. The need and demand for rigorous scientific examination of herbal medicines is the call of the hour to prove compatibility of these constituents in order to combat this deadly syndrome affecting a vast majority of population.

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Microalbuminuria as a Risk Factor for Renal Dysfunction in Diabetic Patients in the British and Saudi Arabia Populations

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Introduction

Microalbuminuria (MA) is considered to be a risk factor for diabetic nephropathy (DN) and progressive renal insufficiency in diabetes for both groups of diabetic patients in UK and Saudi Arabia (1).

Microalbuminuria appears to be a strong predictor of the subsequent development of overt diabetic nephropathy and it is often defined as the excretion of at least 100 mg of albumin per day (2).

Diabetic nephropathy constitutes the most common cause of end stage Renal disease (ESRD) and constitutes the major workload of dialysis centres worldwide. (1,3)

In one of the selected Diabetic studies nephropathy is the cause of 20% of 500,000 diabetic patients registered on renal replacement therapy (4,5).

End stage renal disease (renal failure) in the USA, UK, Japan and most of industrialized Europe, diabetes is the leading cause of renal failure (2).

The costs of dialysis and renal transplantation caused by ESRD implicate a considerable load on health care resources and seriously compromises both the quality of life and life expectancy (3).

Primary prevention of DN is possible if the factors that initiate the change from normal urinary albumin excretion to MA and from MA to DN can be identified and treated (4, 5).

Cross - sectional and longitudinal studies performed in Diabetic patients have shown risk factors associated with the development of microalbuminuria and with progression of microalbuminuria to renal failure in both groups of patients in UK and Saudi Arabia, with significant variable rates (1, 6).

Abstract

Diabetic Nephropathy is the most common cause of end renal failure worldwide.

Microalbuminuria is considered to be the first risk of Diabetic Nephropathy, which can be prevented and treated at early stage. Slight elevation of protein albumin level in the urine could be one of the earlier signs of diabetic nephropathy.

Microalbuminuria increases the risk of cardiovascular disease in diabetic and hypertension patients.

Microalbuminuria is more common in poorly controlled diabetic patients with high blood pressure, and a very clear risk factor for renal dysfunction. For incidence of Microalbuminuria where systolic blood pressure, plasma triglycerides and urinary albumin, antihypertensive drugs have been shown to reduce factors of Microalbuminuria and renal dysfunction.

Key words: microalbuminuria, renal dysfunction, Britain, Saudi Arabia

The factors predisposing to diabetic nephropathy include lower BMI, longer duration of diabetes, hyperglycaemia, hypertension, dyslipidaemia, cigarette smoking, and family history of hypertension (8).

Microalbuminuria is common in poorly controlled diabetic patients with essential hypertension. It is considered to be the first clinically easy identifiable sign of risk of diabetic nephropathy, which can be prevented and treated at an early stage (6,7).

Microalbuminuria is an obvious risk factor for renal dysfunction in diabetic patients, but not in all patients with type 2 diabetes is it the leading cause of end-stage renal disease (ESRD) in the western world (8, 9). Many, but not all patients with type 2 diabetes develop renal dysfunction during their lifetime (6).

In the U.K. in a prospective Diabetes study about 24.9% of British patients developed microalbuminuria within 10 years of diagnosis of type 2 diabetes, while in Saudi diabetic patients it is about 45% (10,11). In Saudi patients who developed microalbuminuria there are no accurate studies about the patients who developed ESRD and only 0.8% in UK patients, as assessed by elevated plasma creatinine (>250 Mmol/L) or the need for renal replacement therapy (2,3).

Clinical diabetic nephropathy with proteinuria, hypertension and decrease renal function developed in Saudi diabetic patients around 45%, 10-15 years from the initial diagnosis of diabetes (11).

Annual rates of transition between successive stages within the classical paradigm of normoalbuminuria to microalbuminuria to macroalbuminuria to ESRD were in the range of 2 - 3% per year in British patients, suggesting that many individuals will not necessarily progress to worsening renal outcomes, even after developing microalbuminuria(6).

On the other hand there are no accurate statistical records of Saudi diabetic patients with annual transition between stages of albuminuria who developed ESRD (3,4,5).

The ability to identify the diabetic patients most likely to progress to poor renal outcomes would allow the institution of appropriate interventions in a timely matter (4).

Microalbuminuria shows that over a median of 15 years after diagnosis of type 2 diabetes, 38% of British participants developed albuminuria and 29% developed renal impairment, while the Saudi participants came up on average 10% higher than the British participants (3, 15).

Importantly, a substantial proportion of patients developed one outcome but not the other. Whereas systolic blood pressure, urinary albumin excretion, and plasma creatinine were risk factors for both albuminuria and renal impairment, other risk factors for these two outcomes were distinct (4,5).

These findings are consistent with the concept that albuminuria and renal impairment may not necessarily reflect the same underlying pathology in type 2 diabetes (10).

In this study in the British patients 15 years after the diagnosis of diabetes, 45.2% of participants had developed albuminuria. Although confirming the high risk of albuminuria in patients with type 2 diabetes, this analysis also demonstrates a high incidence (29%) of renal impairment in this patient population (14,15).

In a UK study, a significant degree of discordance between development of albuminuria and renal impairment is apparent. Of those patients who developed renal impairment, 61 % did not have albuminuria beforehand and 39% never developed albuminuria during the study. Of the patients who developed albuminuria, only 24% subsequently developed renal impairment during the study (15).

These data thus do not support the classical paradigm of albuminuria always preceding renal impairment in the progression of diabetic kidney disease (13,14,15).

In a Saudi study, the prevalence of end stage renal disease (ESRD) as a subsequence of microalbuminuria is similar in both diabetic patients with type 1 & 2 diabetes, when equal duration of the disease was compared (5, 11).

Albuminuria is used clinically as a marker of nephropathic risk in type 2 diabetes. However, it has recently been recognized that the probability of progression to macroalbuminuria in subjects is not as high as once believed, and both stabilization of microalbuminuria without progression and regression of albuminuria are observed. (5,7)

These findings suggest that microalbuminuria alone may not provide absolute identifications of patients with type 2 diabetes at higher risk of renal impairment, and thus identifications of other risk factors is needed (4).

Differentiations need to be drawn between risk factors for albuminuria and those for renal impairment (9).

The most highly associated risk factors for incident albuminuria were systolic blood pressure, plasma triglycerides, and urinary albumin (16).

The central importance of blood pressure as a risk factor for both albuminuria and renal impairment in type 2 diabetes has been well documented in previous observational studies (10).

Antihypertensive therapy has been shown to reduce the incidence of albuminuria and preserve renal function in clinical trials, for both British and Saudi patients (8-10).

In Saudi Arabia, aggressive antihypertensive therapy of diabetic patients with microalbuminuria has been associated with an obvious reduction in albumin excretion and preservation of renal function (4, 5).

Compared with previous studies in type 2 diabetes, the current analysis involves a larger patient population in the UK with longer follow-up and extensive clinical and metabolic characterization, allowing for more complete factors to be controlled (16).

In addition fasting plasma triglyceride concentration consistently appeared as a strong association factor of both microalbuminuria and macroalbuminuria (10).

The current findings support a role for hypertriglyceridemia in the early pathophysiology of albuminuria in type 2 diabetes (12).

Other studies have identified baseline urinary albumin as an independent risk factor for the development of albuminuria and renal impairment (15).

An increased incidence of renal failure has been estimated previously in British patients with type 2 diabetes (15).

The current report confirms these earlier observations and demonstrations that British patients are associated with the development of both albuminuria and renal insufficiency in type 2 diabetes (14, 15).

Previous prospective studies have identified several other risk factors for incident albuminuria in type 2 diabetes, including age, male sex, duration of diabetes, smoking, obesity, and the presence of retinopathy (17).

Although confirming the multifactor nature of the risk profile underlying albuminuria, the current analysis has also identified white cell count as another risk factor for microalbuminuria, though not for macroalbuminuria. This finding raises the possibility that sub clinical inflammation may contribute to incident albuminuria (19, 22).

Three studies have reported a cross-sectional association between peripheral leukocyte count and

urinary albumin excretion in type 2 diabetes (22).

The current report demonstrates additionally a relationship between baseline white cell count and incident microalbuminuria. Although the biological mechanisms underlying this association remain to be cleared, it should be noted that activated leukocytes secrete a variety of potentially nephrotoxic cytokines and can promote oxidative stress (20, 22).

The most highly associated risk factors for creatinine clearance <60 ml/min per 1.73 m² were plasma creatinine, systolic blood pressure, age, female sex, height, and decreased waist circumference. Both serum creatinine and blood pressure have been associated with the development of renal impairment in previous studies (5, 16).

Risk factors for albuminuria and renal impairment in the current analysis, as urinary albumin, the associations with sex and waist circumference highlight the differences between the risk factor profiles for albuminuria and renal insufficiency (16).

The sex and waist circumference exhibited paradoxical associations with these outcomes, with male sex and increased central obesity linked to albuminuria and with female sex and decreased waist circumference associated with renal impairment (23).

Although the basis for these differences is not clear, the discordance between their respective risk factor profiles may reflect pathophysiological differences between albuminuria and renal impairment (15, 16).

Conclusion

Strengths of this study in UK patients include the prospective design, which ensured that measurement of risk factors preceded the development of albuminuria and renal impairment; the recruitment of patients was at diagnosis of diabetes, such that the risk factors identified may reflect early events in the patho-physiology

of renal disease; and the large study population and long follow-up, which provided sufficient power to evaluate numerous risk factors (15-17).

In the UK diabetic patients blood pressure control study showed no difference in the efficacy of captopril and atenolol in reducing the incidence of diabetes complications, including albuminuria (23, 24).

A potential limitation of the current study in the UK is the lack of ability to account for possible regression of albuminuria over time.

A second limitation is that the use of angiotensin converting enzyme inhibitors (ACE) inhibitors was not addressed specifically in this analysis. ACE inhibition has been associated with a decreased incidence of microalbuminuria in patients with type 2 diabetes and hypertension (24).

The reasons for the limitations of this study in Saudi Arabia diabetic patients are the following:

- There are a limited number of patients recruited for this study.
- Short duration of follow up to diabetic patients with microalbuminuria.
- Availability of recent and reliable statistical records in many hospitals.
- Few studies were performed in diabetic complications in particular diabetic microalbuminuria and nephropathy (4,5,11).

Finally in a median of 15 years from diagnosis of type 2 diabetes, nearly 40% of British patients developed microalbuminuria and nearly 30% developed renal impairment, and in Saudi diabetic patients were about 10% higher for both microalbuminuria and renal impairment compared to the British diabetic participants (4, 5, 11).

The above highest percentages in Saudi diabetic patients who developed albuminuria and renal impairment might reflect the deficiency of knowledge and health education of patients about diabetes and its serious consequences and complications (4,5).

Considerable percentage of undiagnosed diabetic patients comes eventually with end stage renal disease and negligence of diagnosed diabetic patients to the appropriate treatments and proper follow up as Hb1c, explained the higher percentage of Saudi diabetic patients with microalbuminuria and diabetic nephropathy, compared to British diabetic patients (11,15).

In addition there is lack of good diabetic services and in coordination with other medical specialists especially renal units (11, 13).

Recommendations

Screening diabetic patients for microalbuminuria identifies those who may benefit from treatments that delay progression to renal failure.

Patients with diabetes mellitus have a 20% to 40% lifetime risk for development of nephropathy, and microalbuminuria is the earliest easily detectable marker of renal damage (25).

Improved control of blood sugar and blood pressure decreases, but does not completely prevent development of microalbuminuria and progression to complete renal failure (26,27,28).

Captopril and Losartan have been shown to diminish this progression even in the absence of hypertension (the latter in type 2 diabetes only).

Blood pressure control and Captopril improve mortality and morbidity for patients with diabetes mellitus type 2. Therefore maximize Captopril or Losartan doses, as tolerated, and aim for a blood pressure of 110-120/70-80 mmHg is the maximum.

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Assessing Children's Knowledge and the Impact of a Specific Health Awareness Program on the Weight Status of Overweight Children in Erbil City

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Introduction

Childhood obesity is largely preventable through lifestyle changes. In general, efforts need to be directed at both dietary intake and physical activities. It has been shown that focusing on reducing sedentary behavior and encouraging free play has been more effective than focusing on forced exercise or reducing food intake in preventing already obese children from gaining more weight(1).

To prevent obesity, it is crucial to involve the whole family; where they shop, what they buy, and how they cook. Developing interventions that encourage children to choose more types of fruits and vegetables requires considerations of psychological factors that are often overlooked(2).

Parents need advice on a variety of topics, and most importantly, is that before parents can be expected to change their own behavior and that of their children, they require an enabling environment - meaning that government polices and organizations must provide them with adequate support(3).

Organizational level factors can include any organization that has an impact on the health problem in question. In the case of childhood obesity, however, the most obvious organization that has an impact is the school. In fact, children and adolescents are in a sense a "captive audience" during the hours of each day they are at school. WHO recommends schools as an important venue in tackling childhood obesity. It rates schools as a "probable" causative factor in relation to obesity. Therefore, it might seem obvious that any intervention regarding childhood obesity should utilize the school as a mode of intervention(4).

Abstract

Background and Objectives:

WHO recommends schools as an important venue in tackling childhood obesity. It rates schools as a "probable" causative factor in relation to obesity. However, interventions at the family or school level will need to be matched by changes in the social and cultural context for a sustained and enhanced benefit. This study mainly aims at assessing the impact of a specific health awareness program on the weight status of the overweight school children.

Methods: Out of 1200 basic education school children, 89 (47 males and 42 females) were identified as overweight and later on involved in a health awareness program using a health education booklet. Three months later, weight of the overweight children was measured again plus that of a number of normal weight children for comparison purposes.

Results: The study revealed that health awareness program had no significant weight reduction impact on the total overweight children compared to normal weight children.

Conclusion: Multi-level integrated actions need to be taken by schools and the community as a whole, emphasizing the importance of controlling the risk factors and managing childhood obesity.

Key words: Obesity, childhood, impact, health awareness.

Interventions at the family or school level will need to be matched by changes in the social and cultural context so that the benefits can be sustained and enhanced. Such prevention strategies will require a coordinated effort between the medical community, health administrators, teachers, parents, food producers and processors, retailers and caterers, advertisers and the media, recreation and sport planners, urban architects, city planners, politicians and legislators(5). Management of obesity in children differs from that in adults in that the prevention of weight gain is important rather than focusing on weight loss. The best and most effective way to treat children with obesity is to treat the family, and not the child alone, by encouraging increased daily activity and healthy eating habits(6).

Both organized and unorganized sport and physical activities are negatively associated with being overweight (10-24% reduced risk) or obese (23-43% reduced risk), while TV watching and video games use are risk factors for being overweight (17-44% increased risk) or obese (10-61% increased risk). Physical activity and sedentary behavior partially account for the association of high socio-economic status and two-parent family structure with the likelihood of being overweight or obese(7).

In general, studies on assessing the impact of an interventional education program on reducing children's weight have never been conducted in Erbil city.

Specific Objectives

- To assess children's perception of their own weight and their parent's interference with their eating habits
- To assess the knowledge of children about the health risk of being overweight
- To assess the impact of a specific health education program for the identified overweight children.

Subjects and Methods

A school based cross sectional survey was carried out during the period January 10 to October 15, 2009 on 1,200 (640 girls and 560 boys) students from 30 Basic Education schools in Erbil city.

A structured questionnaire was used for each of the study subjects to collect the required data, mainly on parent's interference with their children's eating habit, children's perception of themselves being overweight, children's awareness of the health risks associated with being overweight, type of health risks and the sources of this knowledge.

After identifying the overweight and obese children through calculating the Body Mass Index of the study sample, a second visit was paid to the 30 targeted schools to implement a specially designed weight reduction health awareness program for these children. This was done through distributing and explaining a health education booklet prepared by the researcher and named "Overweight and Obesity in Children and Adolescents". The content of health education messages which the booklet included, were mostly derived from the WHO website and it covered awareness messages focusing on adopting a new healthy lifestyle, mainly with regard to diet and physical activities, at home and school. The booklet was produced in two local languages, Kurdish and Arabic, and it contains a number of pictures which have elaborated the good and bad things in relation to diet and physical activity.

The concerned teaching staff who were involved in this stage of the research with overweight and obese children across the 30 schools, were all included with the exception of class-nine children. The reason behind that was that these children have finished basic education and joined secondary schools with the beginning of the new school year (2009/2010), and the fact that it was practically difficult to follow the secondary schools that these children will join next year.

The next stage of this study was achieved after the end of the summer holiday and the start of a new school year, at least three months following the health education session for the overweight and obese children. This stage included another data collection work, but this time focusing just on measuring the weight of children. At this stage the sample was divided into two groups; a first group included overweight and obese children of the studied sample in their schools and a second group of normal weight children as control group obtained from these schools. In each of the target schools a randomly selected similar number of normal weight children to that of overweight children was taken for comparison purposes.

Chi-square (χ^2) was used to identify any kind of association between different variables in the study. P-value was also used to assess the statistical significance of the results obtained; a value of ≤ 0.05 was considered as statistically significant.

Results

1. Parent's interference with children's food intake

Table 1 shows that parents don't interfere with their children's amount and frequency of eating in 58% of overweight children, while in more than 40% of them, parents discourage them from eating and only in 1.5% of overweight children, their parents still encourage them to eat. ($P < 0.001$)

2. Children's perception of their body weight status

About 78% of children who appeared to be overweight have the perception of being overweight or obese, while the remaining 22% of them still don't think that they suffer from increased body weight or obesity, as is obvious from Table 2. ($P < 0.001$)

3. Children's awareness level about overweight

3.1 Children's awareness about the health risks of overweight

Despite more than 95% of children who are overweight know that overweight or obesity is associated with health risks, they are still

Parent's Interference with children's eating	Normal Weight No. (%)	Overweight No. (%)	Chi-Square (df)	P
Encourage	196 (18.3)	2 (1.5)	148.47 (2)	< 0.001
Discourage	74 (6.9)	53 (40.5)		
Don't Interfere	799 (74.7)	76 (58.0)		

Table 1: Distribution of weight status of children in relation to parent's interference with children's eating

Children's perception of themselves being overweight	Normal Weight No. (%)	Overweight No. (%)	Chi-Square (df)	P
No	873 (81.7)	29 (22.1)	221.537 (1)	< 0.001
Yes	196 (18.3)	102 (77.9)		

Table 2: Distribution of weight status of children in relation to their perception of their body weight status

Children's awareness of the health risk of overweight	Normal Weight No. (%)	Overweight No. (%)	Chi-Square (df)	P
No	80 (7.5)	6 (4.6)	1.479 (1)	0.224
Yes	989 (88.8)	125 (95.4)		

Table 3: Distribution of weight status of children in relation to their awareness about whether overweight or obesity might carry a health risk

overweight. Only 4.6% of overweight children don't have any awareness of the health risks overweight might be associated with, as is shown in Table 3. (P=0.224)

3.2 Specification of the Health Risks associated with being overweight

The two main health risks emphasized by children in relation to being overweight or obese were DM and heart diseases in general. Dyspnea, effect on general health, as perceived by children, hypertension, malaise and increased body fat

or cholesterol come in the second priority. Joint pain and backache, cancer and GIT problems come later.

3.3 The source of children's awareness about the health risk of overweight

From Figure 2, it is clear that TV is the major source of awareness of the health risks consequences of overweight for children. Family members, health care facilities come next, followed by people in general, school including teachers, books, etc and newspaper as other less important sources.

3.4 Effect of health awareness program

The health awareness program was conducted only for 89 (47 males and 42 females) among 131 overweight children after excluding 42 children of class nine who left their schools and joined secondary schools. Among the 89 children, it was only possible to measure the effect of the health awareness program on 78 children (42 males and 36 females) since 11 children (five males and 6 females) have left their schools for different reasons.

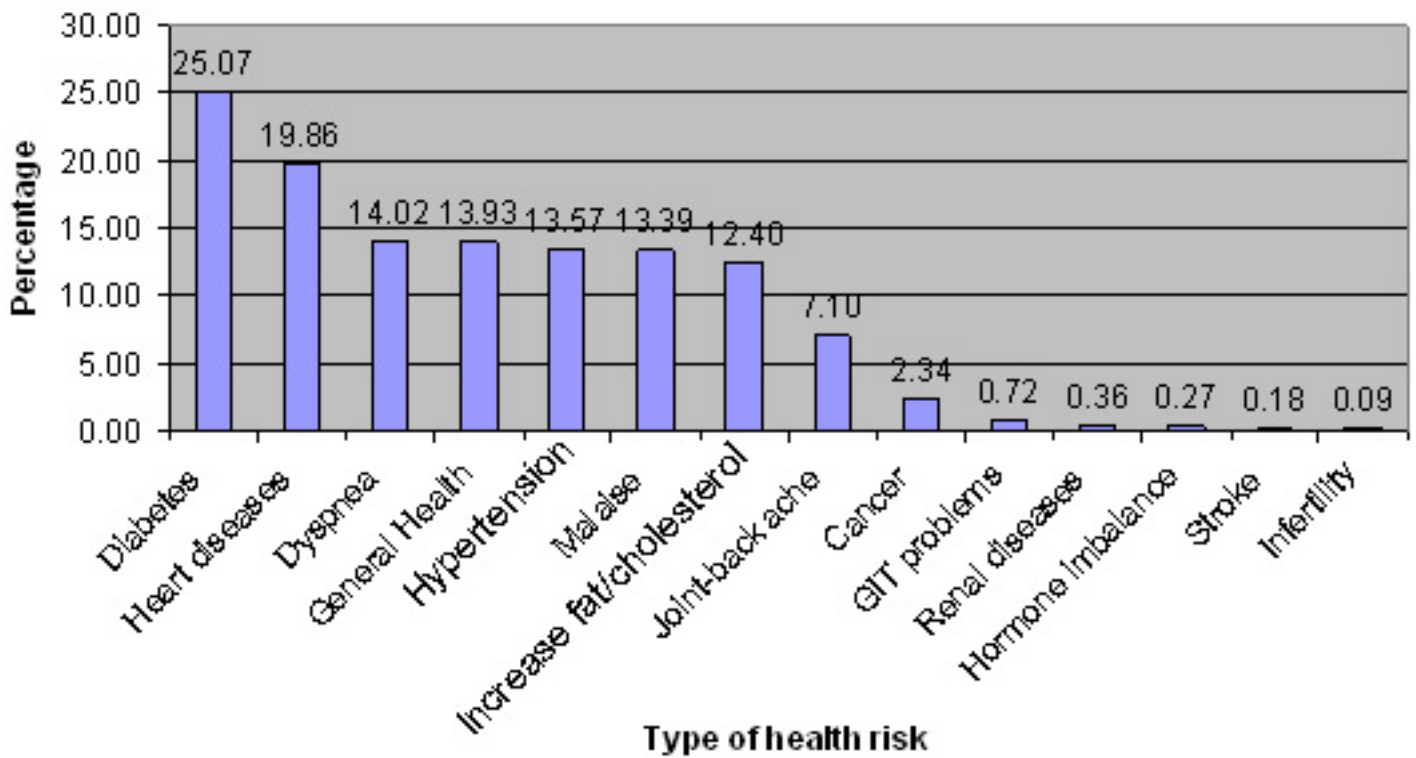
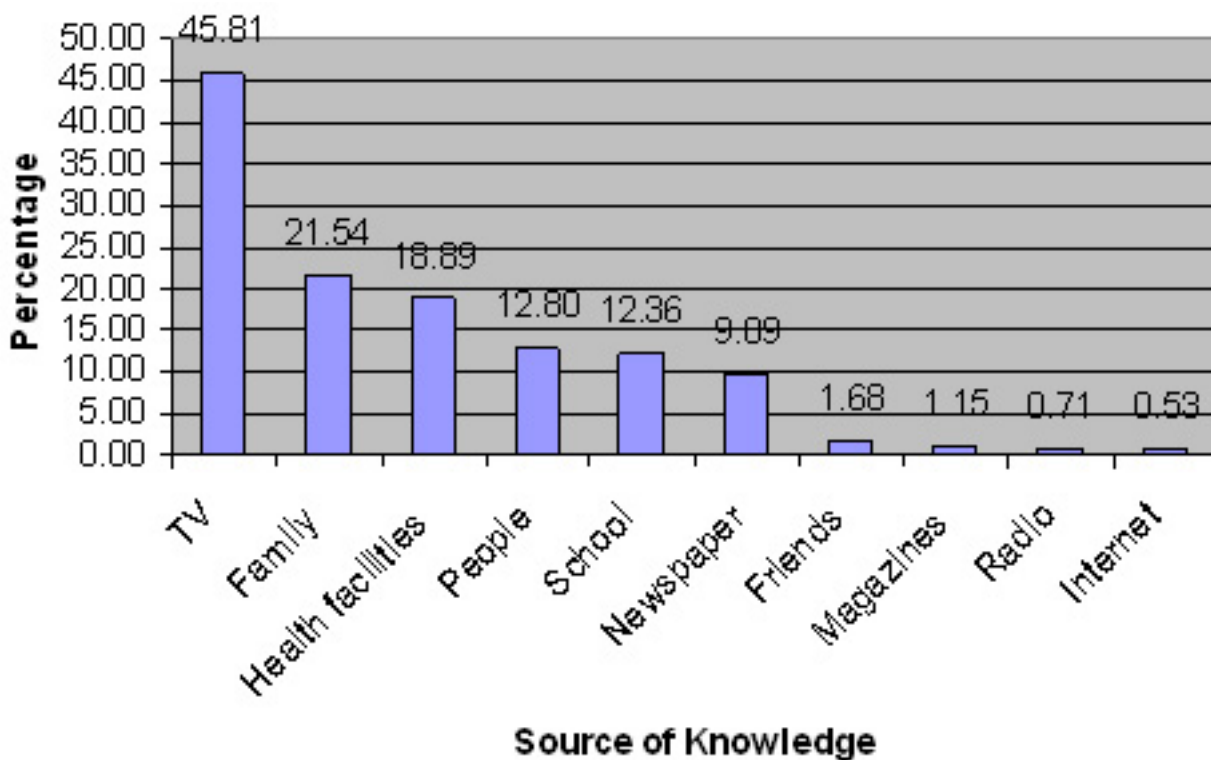


Figure 1: Distribution of health risks related to being overweight as perceived by children



Note: most children had more than one answer

Figure 2: Distribution of children in relation to the source of knowledge of the health risk consequences of overweight

	Males **		Females ***		Total *	
	Obese No. (%)	Control No. (%)	Obese No. (%)	Control No. (%)	Obese No. (%)	Control No. (%)
Decreased Weight	12 (28.57)	13 (30.95)	22 (61.11)	15 (41.67)	34 (43.59)	28 (35.90)
Increased Weight	30 (71.43)	29 (69.05)	14 (38.89)	21 (58.33)	44 (56.41)	50 (64.10)
Total	42 (100%)	42 (100%)	36 (100%)	36 (100%)	78 (100%)	78 (100%)

* Chi Square = 0.96 P = 0.326 (Comparison between Overweight and Control Among total group of children)

** Chi Square = 0.66 P = 0.811 (Comparison between Overweight and Control Among Males)

*** Chi Square = 2.72 P = 0.098 (Comparison between Overweight and Control Among Females)

Table 4: Comparison between weight status of overweight children and controls among males, females and total group, following health awareness program for overweight children

Results of the third part data collection which was conducted at the beginning of 2009-2010 school year program to show the effect of the awareness program conducted for overweight children in the previous school year, showed that only 43.59% of the total overweight children have decreased weight during the summer holiday compared to only 35.89% of the total control group (normal weight children) who decreased weight during summer holiday even without being included in the health education program, (P = 0.326) as is shown in Table 4. Concerning male children, 28.57% have decreased weight among overweight compared to 30.95% among controls, (P = 0.811), and with regard to female children, 61.11% of overweight female children have decreased weight compared to 41.67% of control female children, (P = 0.098).

Results also showed that among overweight children, the mean weight before receiving health education was (73.4295) kilograms and that of after health education was (73.5436)

kilograms with (P = 0.742), while among the control group who didn't receive health education, the mean weight before the summer holiday was (52.6654) kilograms and that after the summer holiday was (53.4641) kilograms with (P = 0.007).

Discussion

In general, overweight and obesity are assumed to be the results of an increase in caloric and fat intake. On the other hand, there is supporting evidence that excessive sugar intake by soft drinks, increased portion size, and steady decline in physical activity have been playing major roles in the rising rates of obesity all around the world. Consequently, both over-consumption of calories and reduced physical activity are involved in childhood obesity (8).

In Iraq, relatively little information is available on the problem of childhood obesity, apart from a couple of examples of research conducted in Baghdad(9), and Babil Governorates(10). The same is applied to the Kurdistan region since the only study conducted in

this regard was the one in Duhok Governorate in 2006(11). This study assessed the effect of a school-based health awareness program especially targeting overweight and obese children using health education messages focusing mainly on calories intake and physical activity.

The study revealed that there is a significant association between the weight status of children and their parents' interference with their food intake. Among overweight children, 58% their parents don't interfere with the amount and frequency of food taken by their children compared to 40.5% where parents discourage them and 1.5% where parents still encourage their overweight children to take food. These results reflect the parental perception about the weight status of their children which can, in addition to other factors, play an important role in shaping the weight of their children. A study conducted in the United States revealed that parental control over children's food intake was inversely associated with overweight among 3rd grade girl

students (weak and significant), but no relationship between parental control of children's intake and their children's degree of overweight was found among boys(12). Another study conducted on 4-12 years old children in Bayamon, Peru Republic, showed that the majority of parents do not perceive their children at risk of becoming overweight or being overweight; 33% of parents do nothing about their children's weight and consider themselves to be responsible for childhood obesity(13).

The study results revealed that about 78% of children who appeared to be overweight have the perception of being overweight or obese compared to 22% of them who still don't think that they are overweight or obese ($P < 0.001$). This might be, especially in our society, an important point to be considered while studying childhood obesity since overweight children who don't perceive themselves as overweight or underestimate their overweight status will not be encouraged to change their dietary or other lifestyle habits on the way of getting an ideal body weight for their age.

Our results also showed that more than 95% of overweight children were aware of the health risks that might be associated with being overweight or obese whether at this age or later on during life compared to less than 5% of overweight children who lack the knowledge about the health risks which overweight or obesity might create, ($P = 0.224$). In order of importance, children thought that the main health risks associated with being overweight or obese are diabetes, heart diseases, dyspnea, effect on general health, hypertension, etc. More than 45% of children stated that they got their awareness regarding the health risks of being overweight or obese from TV followed by family members, health facilities, schools, newspaper, etc.

The study also examined the effect of the health awareness program on weight reduction of the identified overweight children and revealed a weight reduction of 43.59% of overweight children who were

included in such program before the end of 2008-2009 school year compared to 35.90% of a control of the normal weight children group who didn't benefit from such a program, but the results were not statistically significant, ($P = 0.326$). Results also revealed that 61.11% of overweight females included in the health awareness program have reduced weight compared to 41.67% of control females ($P = 0.098$), and 28.57% of overweight males reduced weight compared to 30.95% of control males ($P = 0.66$). The study also showed that among obese children, the mean weight has slightly increased after health education, but it is statistically insignificant ($P = 0.742$), while among the control group children, the mean weight after summer holiday also increased and it is statistically significant ($P = 0.007$).

The study results are inconsistent with those of a study conducted in United States on intermediate school age children which included school based interdisciplinary intervention to reduce obesity rates among children. In this study health education messages were included in existing curricula using classroom teachers and covered issues like decreased television viewing, decreased consumption of high energy foods, increased fruits and vegetable intake and increased physical activity. This study revealed that the prevalence of obesity among girls in intervention schools was significantly reduced compared with controls with no differences found among boys(14). Our results were also inconsistent with another study conducted on Dutch school teenagers to show the effectiveness of school-based program on the body weight of these teenagers. The health education program included 11 lessons in biology and physical education and showed that the intervention remained significantly effective in preventing unfavorable increase in important measures of body composition in both girls and boys after 20-month follow-up(15).

The health awareness program in our study was conducted using a booklet prepared in both Kurdish and Arabic

languages, and included pictures as means of understanding its content. The health awareness program might have been affected by the fact that the period between the intervention and the re-assessment just included the three-month summer holiday which is relatively short. Children's lifestyles, like the way and amount they eat and the time they spend in sedentary activities, may also change during summer holiday and hence can influence the study results.

Conclusions

Integration of the health education program, focusing on eating healthy foods and practicing physical activities, into the schools' studying system, can have an important role in the prevention of obesity and its adverse risks. The health education messages can be well integrated into the curricula of some lessons like biology and physical activity. Moreover, the children's families can be involved in such programs through the established Parents Teachers Association network.

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Effect of Switching from Free Co-administration of Sulfonylurea and Metformin to Combined Combination of Glibenclamide and Metformin (Glucovance®) on Postprandial Glycemic Control in a Sample of Iraqi Type 2 Diabetics

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Abstract

Objective: To assess the changes in postprandial plasma glucose level in a sample of Iraqi patients with type 2 diabetes switched from free co-administration of metformin and sulfonylurea to a combination of glibenclamide/metformin tablets (Glucovance®).

Method: A retrospective, medical records review was conducted in private diabetic clinic in Baghdad on type 2 diabetic patients initiated on Glibenclamide and Metformin tablets between September 2010 and December 2011. Postprandial plasma glucose was measured two hours after lunch meal. Multiple plasma glucose check-up was taken for each individual, at least three before and three after switching, with the first measure in each case done after not less than one month from starting the regime, and the mean result for each of them was adopted.

Results: Ninety-one patients were enrolled in the current study. At baseline, 78 patients received glibenclamide (85.7%), while the remaining 13 patients (14.3%) were on glimepiride. The mean baseline postprandial plasma glucose in the total population was 317.5 mg/dl. The mean reduction in its level was 91.2 mg/dl ($P < 0.001$) after initiation of Glibenclamide and Metformin. Similar significant individual reduction was seen during subset analysis among those on glibenclamide or glimepiride at baseline. The reduction in postprandial plasma glucose for those on glibenclamide dose within Glucovance® tablets of 2.5 mg/day, 5 mg/day, and 10/day mg was 80.7 mg/dl, 97.7 mg/dl, and 123.8 mg/dl, respectively ($P = 0.062$).

Conclusion: Patients switched from free co-administration of sulfonylurea and metformin to combined combination of glibenclamide and metformin showed marked improvement in postprandial plasma glucose level that was significant regardless of the type of sulfonylurea used previously. This improvement was promoted as the total dose of glibenclamide in combination tablets increased.

Key words: Sulfonylurea, Metformin, Fixed Combination Tablets, Glibenclamide, Glucovance®, Postprandial Plasma Glucose, Type 2 Diabetes.

Introduction

Type 2 diabetes (T2D) carries a heavy burden of disability and death from a wide range of vascular complications associated with long-term hyperglycemia. People with T2D are more prone to retinopathy, peripheral vascular changes, and renal impairment; they have also an increased risk of myocardial infarction and stroke.(1) Those diagnosed with T2D at age 50 and 80 stand to lose up to 10 and 4 years, respectively, of total life expectancy.(2) As the prevalence of T2D continues to rise,(3) management strategy needs to be directed not only towards prevention of disease but also the numerous metabolic abnormalities underlying it and leading to previously mentioned events.

During the natural history of T2D, patients progress from completely normal euglycemia through impaired glucose tolerance to overt hyperglycemia.(4) The core metabolic disorders that have been recognized to play dominant roles in the pathogenesis of this process are insulin resistance and reduced postprandial insulin secretion.(5) Therefore; as long as β cells are capable of secreting sufficient amount of insulin to overcome the encountered insulin resistance, normal glucose tolerance is preserved. Once interruption to this dynamic interaction occurs, progressive deterioration in glucose hemostasis will be the resulted outcome.(4,5)

Data from UK Prospective Diabetes Study (UKPDS) and other research have deduced that at the time of T2D diagnosis, approximately 50% of normal insulin sensitivity and a similar percentage of β -cells function are lost. Consequently, insulin levels are inadequate to compensate for insulin resistance and chronic hyperglycemia ensues.(6,7) The hyperglycemia of T2D worsens over time as deterioration in metabolic activities continues to advance. Thus, oral antidiabetic monotherapy can maintain glycemic control adequately for only the early period and the majority of patients will experience

secondary failure despite the type of drug used initially.(8)

Treatment intensification with a second oral agent is a commonly applied practice to reinforce glycemic control in those who failed with monotherapy and is considered to be more effective than switching to an alternative medication.(9) Giving the multiple pathogenic mechanisms of T2D, using of numerous agents with complementary modes of action represents the most appropriate way to be considered in this status.(7) However, polypharmacy is common among T2D patients and the complex oral diabetic regime may impair compliance and achievement of therapeutic goals.(10) A smart and relatively new solution to this problem is the use of fixed-dose combination tablets that have been associated with higher medication adherence and better glycemic control.(11,12)

The fixed combination glibenclamide-metformin [Glucovance®] tablets are one of the first antidiabetic combinations delivered to the markets.(13) Its components were chosen to be included as they have been examined in randomized clinical trials when used alone or in conjugation.(14) Moreover, these agents are each supported by a long period of clinical experience and each has been proven to reduce the risk of diabetic complications in UKPDS.(6) Finally, their pharmacokinetics and pharmacodynamics are sufficiently compatible to support administration as a combined formulation.(15)

These days, the pandemic of diabetes mellitus has invaded Iraq in a tremendous manner. Thus; while the national data estimated affected adults as around one million in 2010, this number has been predicted to rise to more than 2.5 million by 2030.(3) This figure raises the alarm and indicates the need for recruitment of all possible efforts in order to deal with this situation.

The aim of this study was to assess the changes in postprandial plasma glucose (PPG) level in a sample of Iraqi patients with T2D switched

from free co-administration of metformin and sulfonylurea to combined combination glibenclamide /metformin tablets.

Method

A retrospective, medical records review was conducted in private diabetic clinic in Baghdad on type 2 diabetic patients initiated on Glucovance® tablets between September 2010 and December 2011. For all patients who had a prescription for glibenclamide/metformin tablets, their medical records were checked for suitability of involvement in this study.

Patients aged 18 - 80 years with type 2 diabetes were eligible if they had received Glucovance® therapy for at least three months, had been treated with glimepiride or glibenclamide plus metformin at least six months prior to switching to Glucophage® tablets, and did not exceed the maximum daily dose of 15 mg of glibenclamide, 6 mg of glimepiride, 2000 mg of metformin (preswitch), or 10 mg/1000 mg of Glucovance® tablets (postswitch).

Postprandial plasma glucose was measured two hours after lunch meal. Multiple plasma glucose check-up have been taken for each individual, at least three before and three after switching, with the first measure in each case done after not less than one month from starting the regime, and the mean result for each of them was adopted.

Patients then were excluded if they had any of the following: diabetic ketoacidosis, congestive heart failure, (ejection fraction <40%) requiring pharmacological treatment; acute or chronic metabolic acidosis; renal dysfunction (serum creatinine ≥ 1.5 mg/dl for males and ≥ 1.4 mg/dl for females) or hemodialysis; pregnancy; or concomitant use of either glibenclamide or metformin with Glucophage® tablets.

The inclusion and exclusion criteria were applied in an attempt to allow a critical time period of postprandial plasma glucose to have been stabilized preswitch and postswitch

to Glucovance® tablets, to include only those who received antidiabetic medications at doses approved within each package insert, and to exclude those with treatments or conditions that may affect the glycemic control.

Patients who exhibited a significant change in medication adherence after switching to Glucovance® tablets have been also ruled out, as the current study was directed to investigate the pharmacological effect of these tablets.

Data collected for analysis included: age; sex; diabetes duration; name, frequency, dose, start date and stop date of previous medications used for T2D; time of conversion to Glucovance®, its frequency, and dose; and any associated medical problem or complication. Baseline and follow-up postprandial plasma glucose testing were performed for each patient in the same laboratory. Other prescribed medications were recorded, including lipid-lowering agents and medications that can affect blood glucose level.

Ethics approval was obtained from Institutional Review Board at Iraqi National Diabetes Center. Ninety one patients were identified to be qualified by meeting the required criteria.

Statistical Analysis

All computerized statistical analyses were done by using SPSS/18 program. Demographic and clinical data were computed by slandered descriptive statistic. Changes in plasma glucose before and after switching to Glucovance were analyzed using paired t test and the patients served as their own controls. The comparison of effect of different doses per day of glibenclamide within Glucovance on magnitude of change in PPG was performed by application of the analysis of variance (ANOVA) test.

The cut-off value between recommended and poor PPG level was selected at 180 mg/dl according to the American Diabetes Association standard of medical care-2011.(16) Medication adherence rate was

calculated by the number of days of therapy supplied divided by the number of days in treatment. Results were considered statistically significant at p-value less than 0.05.

Results

As mentioned previously, 91 patients were enrolled in the current study. Those individuals were predominantly females (69.2%), with an average age of 51.8 years. Patients had been diagnosed with diabetes, on average, 6.35 years prior to involvement in the study (Table 1). At baseline, 78 patients received glibenclamide (85.7%), while the remaining 13 patients (14.3%) were on glimepiride. Mean daily doses of glibenclamide and glimepiride at baseline were 7.72 mg and 2.77 mg, respectively; while the mean glibenclamide dose at final follow-up was 4.18 mg. Comparable doses of metformin were used during the whole time of the study.

All patients had preswitching poor glycemic control as measured by postprandial plasma glucose level, i.e. PPG \geq 180 mg/dl. After conversion to Glucovance®, 26 patients (28.6%) have been brought to accepted glycemic control.

The mean baseline postprandial plasma glucose (PPG) in the total population was 317.5 mg/dl. The mean reduction in PPG was 91.2 mg/dl ($P < 0.001$) after initiation of Glucovance® (Figure 1).

Similar significance of individual reduction in PPG was seen during subset analysis among those on glibenclamide or glimepiride at baseline (Table 2 - page 20). These cohorts experienced a mean reduction of 92.3 mg/dl for those on glibenclamide ($P < 0.001$), and 85.2 mg/dl for those on glimepiride ($P = 0.001$).

To examine the effect of increased Glucovance® dose on further improvement in plasma glucose, additional analysis was performed with segregation of patients according to the given dose of glibenclamide within Glucovance® tablets (Table 3 - page 20). The

reduction in PPG for those on dose of 2.5 mg/day, 5 mg/day, and 10/ day mg was 80.7 mg/dl, 97.7 mg/dl, and 123.8 mg/dl, respectively. Accordingly, these results showed some association with borderline significance ($P = 0.062$).

Discussion

This study explores a relatively new technique in the management of T2D, the possibility of using fixed-dose combination tablets to achieve better glycemic control. It shows a significant improvement in PPG in those switched from sulfonylurea co-administered with metformin to glibenclamide-metformin (Glucovance®) tablets. This amelioration was statistically significant irrespective of type of sulfonylurea used before. There was also an enhancement in magnitude of improvement as the dose-strength of glibenclamide within combination tablets increase. From all patients who were formerly with uncontrolled postprandial hyperglycemia, more than one-fourth have been brought to the recommended PPG target after switching to Glucovance®.

Considering the database of different researchers showing that PPG is a better index of glucose regulation and predictors of glycemic control than fasting plasma glucose, the clinical implications of the current study become more important and valuable work. Additionally, normal/near-normal PPG levels are associated with lower rates of cardiovascular complications and all-cause mortality than elevated post-challenge hyperglycemia.(17,18) Post-prandial hyperglycemia and spikes possess also a deleterious effect on insulin secretion and sensitivity.(19)

Information extracted from previous articles has revealed promising results regarding the usage of Glucovance®. This combination tablet has been found to be associated with a better glycemic control, as measured by glycated hemoglobin (HbA1c) value, than utilizing its components, either as a monotherapy(20-22) or free co-administration tablets.(23,24) It was also linked with an important

No. of patients	91
Female sex, n(%)	63(69.2)
Age, mean(±SD)	51.8(10.2years)
Duration of T2D, mean(±SD)	6.35(3.93years)
Types of antidiabetics used at baseline, n(%)	
Glibenclamide + Metformin	78(85.7)
Glimepiride + Metformin	13(14.3)
Dose of antidiabetics at baseline, mean(±SD)	
Glibenclamide	7.72(4.40mg)
Glimepiride	2.77(2.14mg)
Dose of Glibenclamide after switching, mean(±SD)	
for all patients	4.18(2.88mg)
for those on Glibenclamide from baseline	4.20(2.33mg)
Patients within recommended PPG at final follow-up, n(%)	26(28.6)

Table 1: Clinico-epidemiological Characteristics of Study Sample

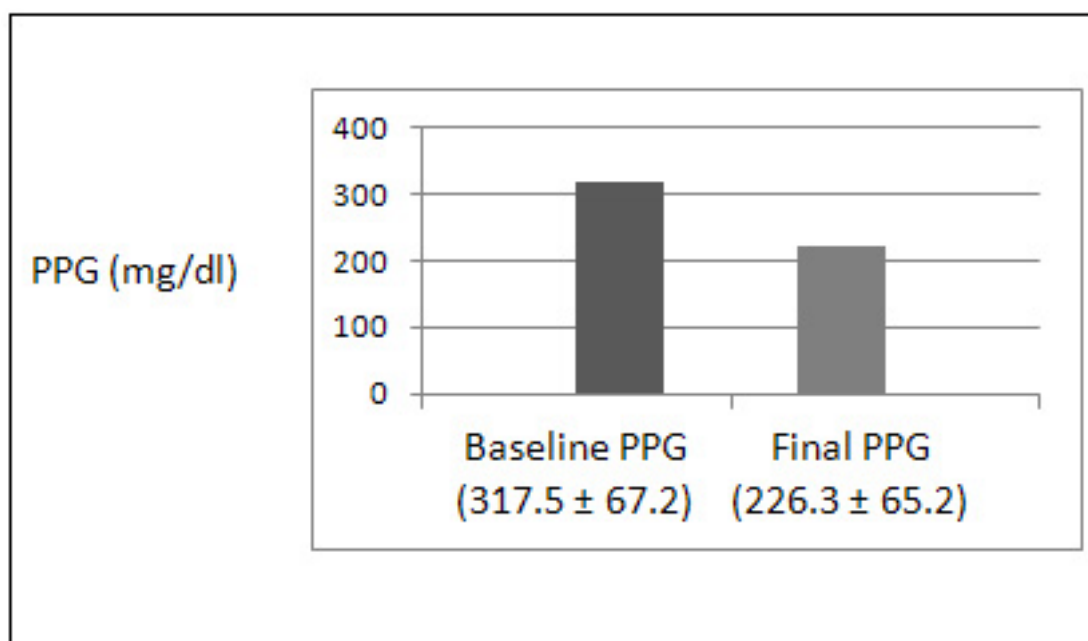


Figure 1: Change in Postprandial Plasma Glucose (PPG) in mg/dl after Glucovance® usage (p<0.001)

Type of Sulfonylurea	PPG (in mg/dl) at Baseline mean(±SD)	PPG (in mg/dl) at Final Follow-up mean(±SD)	Δ PPG (in mg/dl) mean(±SD)	Significance
Glibenclamide	316.2(69.4)	223.9(66.7)	92.3(58.6)	<0.001
Glimepiride	325.6(53.3)	240.4(55.4)	85.2(68.5)	0.001
Total	317.5(67.2)	226.3(65.2)	91.3(59.7)	<0.001

Table 2: Effects of Switching on Post-prandial Plasma Glucose (PPG) Levels According to Type of Sulfonylurea Used at Baseline

Dose of Glibenclamide in Glucovance	No.(%) of patients on the Dose	PPG (in mg/dl) at Baseline mean(±SD)	PPG (in mg/dl) at Final Follow-up mean(±SD)	Δ PPG (in mg/dl) mean(±SD)
2.5 mg/day	53(58.2)	313.9(67.4)	233.2(66.9)	80.7(54.8)
5 mg/day	26(28.6)	332.1(70.0)	234.4(62.3)	97.7(69.4)
10 mg/day	12(13.2)	301.8 (58.7)	178.0(43.4)	123.8(48.1)
Significance:		P =0.062		

Table 3: Relationship between the Daily Dose of Glibenclamide within the Glucovance® tablets and the Degree of Change in Post-prandial Plasma Glucose (PPG) Levels

increase in patient compliance as compared to two-pill therapy.(12,13) In addition to that, the incidence of reported gastrointestinal side effects were significantly fewer compared with metformin alone in diet failed patients and comparable in post-monotherapy studies.(25) However, still other studies pointed to some restrictions like higher prevalence of hypoglycemia as compared to sulfonylurea monotherapy,(20,21) which indicates the need orf further research on this drug.

The mechanism of action through which Glucovance® manifests its additive hypoglycemic effects was explained by increasing insulin secretion.(26) Glibenclamide plays the major role in this process as it has been absorbed more rapidly from combination tablets than from glibenclamide tablets given separately with metformin. On the other side, metformin plasma concentrations were found to be similar in both treatment regimens and its role was expected to be

restricted on facilitate absorption of glibenclamide within Glucovance.(27)

The combination tablets contain glibenclamide in a precisely controlled range of particle sizes included within a freely-soluble metformin matrix. This design is thought to influence the rate of absorption of glibenclamide into the bloodstream and help to control post-prandial hyperglycemia more effectively following administration with meal.(28)

In such as our study design, it is important to consider the effect of all confounders that may affect the outcome. Consequently, the specific role of individual sulfonylurea used before switching was examined. The inferred improvement in PPG level in patients on either medication, whether glibenclamide or glimepiride, may indicate the possibilities of taking the advantage of switching to Glucovance® for patients who were previously on other sulfonylureas. Nevertheless, this remains

theoretical and the need for more clinical research is mandatory.

Additional subset analysis was done for those receiving glibenclamide within their initial treatment. This action was performed to determine whether change in dose of that medication, before and after switching, may contribute to improvement in PPG level. The result of this analysis has abolished such an idea as the mean daily dosage of glibenclamide decreased, rather than increased, after switching. This present finding is in consistent with the findings obtained by Dailey GE, which suggested that the combination tablets control glycated hemoglobin (A1c) more effectively and at a lower mean doses of glibenclamide and metformin than free co-administration of them.(29) This point may provide a rational explanation to the lower incidence of side effects reported with combination tablet approach than separate components therapy.

The observed improvement of PPG level as the total dose of glibenclamide in Glucovance® increase supports the finding of Brunetti et al,(30) which mentioned that combination tablets containing 5-mg glibenclamide produced greater reduction in post-prandial glycemic control compared with fixed tablets containing 2.5-mg glibenclamide. The problem of a small proportion of patients in the current study who attained the recommended PPG target may find its solution here. Thus, patients on the highest dose of glibenclamide, i.e. 10-mg, have a mean PPG value lying within the recommended level, and the increase in dose could be applied to others as long as there is no contraindication for it.

Limitations of the study

The relatively small number of patients enrolled in this study may represent the major constraint for generalization of its results. The strict inclusion and exclusion criteria proposed in the required sample would limit the qualified records. These actions were undertaken to eliminate the contribution of confounding factors which may affect the results and decrease their validity.

The dependence of the study sample on patients attending the private sector may represent a factor that could restrict the quality of patients. Those patients depended on their own budgets in covering the price of this medication which may be costly for others.

The study has concentrated its analysis and discussion on glibenclamide component within Glucovance® as the beneficial effect has been proposed to depend mainly on the specific formulation and action of this drug within the combination tablets. Nevertheless, metformin is certainly has a certain role which should be sought in coming works.

Finally, the use of PPG level alone is not enough in assessing the efficacy of Glucovance® in glycemic control. Other measures should be scanned, e.g. fasting plasma glucose and

glycated hemoglobin that represent a scope for future research.

Conclusion

Patients switched from free co-administration of sulfonylurea and metformin to combined combination of glibenclamide and metformin showed marked improvement in PPG level that was significant regardless of the type of sulfonylurea used previously. This improvement was promoted as the total dose of glibenclamide in combination tablets increased.

Traditionally, patients who report failure of control of hyperglycemia with oral antidiabetic agents can overcome this situation by increasing dose of drugs, adding of a new drug, or shifting to insulin. The use of fixed combination of the same drugs represents a good idea that provides the opportunity to fight diabetes with the same weapons and comparable firepower but with a new strategy. This plan could be expanded to be included within diabetes management guidelines.

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RABI - An Acronym to Aid Critical Appraisal of Validity

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Introduction

Evidence-based medicine (EBM) is the practice of assessing the medical literature in a time-efficient manner to answer a clinical question about a certain condition[1]. Medical literature may be biased because of the internal validity of studies being compromised by different forms of measurement error[2].

EBM practice comprises 5 A's [3-5]:

- (A1)** Asking a clinical question by using the (PICO) format, where (P) stands for population and the problem, (I) for intervention, (C) for comparison or control, and (O) for outcome.
- (A2)** Acquire the evidence from the best available research.
- (A3)** Appraisal of retrieved article,
- (A4)** Applying evidence to the patient,
- (A5)** Assessment of performance.

Critical appraisal is the skill of evaluating the literature to determine whether the article outcomes were influenced by known or unknown sources of bias. Critical appraisal is the bridge between finding relevant data and applying the information to clinical practice which enables health care practitioners to distinguish high from low quality studies and to determine potential problems with the evidence, and help them to decide whether to use or not to use that evidence[2, 4].

Appraisal of medical literature includes evaluating the article for its relevance, validity, results and applicability.

In this section we will describe a new, easy to remember abbreviation, which helps the health care practitioner to appraise the study validity for articles about therapy, systematic review, diagnosis and prognosis.

Abstract

Introduction: Many medical schools and residency programs are teaching critical appraisal of articles, by using worksheets. Teaching critical appraisal of validity requires the instructor to use different worksheets for each type of question, which are difficult to remember and require the learner to have the worksheets on hand. RABI is an acronym developed to appraise the validity of therapy, systematic review, and diagnosis and prognosis articles.

Methods: Items included were derived from user's guide to medical literature, centre of evidence based medicine critical appraisal worksheets, Cochrane risk of bias (ROB) tool and quadas-2 tool. A quantitative evaluation of RABI with the user's guide worksheets in relation to items included and item's sequence. Participants of six three-day evidence based medicine courses were involved in this study.

Results: 217 of 243 (89.3%) participants completed the study. There was no statistical difference between RABI and user's guide to medical literature. Participants believe that it is easy to use and remember.

Discussion: RABI included 24 items that cover the items included at 4 worksheets for therapy, systematic review, diagnosis and prognosis. Compared with user's guide to medical literature, RABI has no statistical difference in terms of items included and sequence and may replace four worksheets.

Conclusion: RABI is an acronym, each letter indicates certain items for the four domain questions, which made it easy to remember and use by teachers and learners.

Key words: RABI, critical appraisal

Validity is the correctness (free of bias); the degree of closeness which iterated results approach the correct result and considers whether the treatment effect reported in the article represents the true direction and magnitude of the treatment effect[6]

RABI is an acronym for validity assessment of articles about therapy, systematic review, diagnosis and prognosis.

Methods

Teaching medical students and residents appraisal concepts is becoming popular at many medical schools. Assessment of EBM sessions is part of the student's assessment. This acronym summarizes the main concepts and items of validity appraisal of articles about therapy, diagnosis, prognosis and systematic review and meta-analysis of therapy.

RABI is required to:

1. Assess the methodological quality of therapy, systematic review, diagnosis and prognosis studies in generic terms (relevant to all such studies)
2. Allow consistent and reliable assessment of quality by medical students, residents and other health care professional with different backgrounds
3. Be relatively short, easy to remember and simple to complete

'Quality' was defined to include the internal validity of a study; the degree to which estimates have not been biased, and the degree to which the results of a study can be applied to patients in practice.

Items were generated from User's guide to medical literature [4, 7-11], Centre for Evidence Based Medicine critical appraisal sheets [12], Cochrane Risk of Bias (ROB) tool [13, 22], and Quadas-2 tool [14, 37, 38].

Quantitative evaluation of RABI:

RABI was compared with the user's guide worksheets; the National and

Gulf Center for Evidence Based Health Practice (NGCEBHP) had conducted 6 three-day appraisal workshops with the main objective to teach participants the critical appraisal skills for articles about therapy, diagnosis, prognosis and systematic review. RABI was described to participants and all were requested to use and rate RABI compared to the user's guide worksheets. Rating of RABI includes: item's included, item sequence and participant's general impressions. Four Likert score was used for rating RABI, Very good, good, fair and poor.

Results

24 items were included as described in Table 1

RABI for validity appraisal of an article about Therapy:

Seven terms are included by RABI, Randomization, Reporting bias, Allocation concealment, Attrition, Balanced groups, Blinding and Intention to treat analysis.

R (Randomization, and Reporting Bias)

Randomization:

It is the process by which the sample population is divided into two balanced groups [1, 6, 7]. Each subject has an equal (50%) chance to be in either group. The process of randomization is more likely to equally distribute known and unknown prognostic factors among the treatment and control groups. In other words both intervention and control groups start with the same[1, 7, 8] prognosis. Known Prognostic factors like age, sex, severity of illness and co-morbidity, and the unknown prognostic factors like genetics and hereditary are more likely to be distributed equally[6, 7]. Randomization is usually done by using a computer that generates a list of random numbers, which can then be used to generate a treatment allocation list. By randomization and concealed allocation the two groups start balanced [1, 6].

Reporting Bias:

Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of results. It includes many biases. Publication bias is the decision of publication or non-publication of research based on the nature and direction of the results but not on research methods. Another reporting bias is Outcome reporting bias. In many studies, a range of outcome measures is recorded in the protocol but not all are reported in the published data. The choice of outcomes that are reported can be influenced by the results, potentially making published results misleading. Such outcome reporting biases may be particularly important for adverse effects. Hemminki examined reports of clinical trials submitted by drug companies to licensing authorities in Finland and Sweden and found that unpublished trials gave information on adverse effects more often than published trials [9]. Since then, several other studies have shown that the reporting of adverse events and safety outcomes in clinical trials is often inadequate and selective [10, 11]. A group from Canada, Denmark and the UK recently pioneered empirical research into the selective reporting of study outcomes [12, 13]. These studies are described in Chapter 8 of Cochrane Handbook, along with a more detailed discussion of outcome reporting bias [14-16]

The table on page 26 summarizes some different types of reporting biases [16].

A (Allocation and Attrition)

Allocation:

Is the assignment of study population to study arms, which should be concealed. Allocation is concealed when those enrolling patients are unaware and cannot control the arm to which the patient is allocated. Neither participants nor researchers know or can predict to which group in a study (control or treatment) the patient is assigned. Allocation concealment takes place before the study begins, as patients are being assigned [1, 7, 8]. In unconcealed

Validity RABI	Therapy	Systematic Review	Diagnosis	Prognosis	Total Items
R	2	2	2	1	7
A	2	3	1	2	8
B	2	1	1	1	5
I	1	1	2		4
Total Items	7	7	6	4	24

Table 1: Number of items included

Validity RABI	Therapy	Systematic Review	Diagnosis	Prognosis
R	<ol style="list-style-type: none"> 1. Randomization (<i>Start Balanced</i>) 2. Reporting Bias (<i>not all outcomes are reported</i>) 	<ol style="list-style-type: none"> 1. Representative sample: Criteria (inclusion and exclusion – Study design – PICOT) 2. Reproducibility: 2 reviewers assess included studies quality 	<ol style="list-style-type: none"> 1. Representative sample: appropriate spectrum of patients 2. Reference standard: Describe it and how it was conducted and interpreted 	<ol style="list-style-type: none"> 1. Representative Sample: (patients assembled at a common (usually early) point in the course of their disease)
A	<ol style="list-style-type: none"> 1. Allocation (concealment) 2. Attrition Bias (follow-up sufficiently long and complete) 	<ol style="list-style-type: none"> 1. Articles' (3 S): Search, Selection & Summary 	<ol style="list-style-type: none"> 1. Ascertained (Verification Bias) 	<ol style="list-style-type: none"> 1. Adjustment of prognostic factors 2. Attrition bias (follow-up sufficiently long and complete)
B	<ol style="list-style-type: none"> 1. Balanced groups (patients' characteristics) 2. Blinding & (3Cs) <i>Run Balanced</i> 	<ol style="list-style-type: none"> 1. Blind Articles' quality assessment 	<ol style="list-style-type: none"> 1. Blind Comparison of index test result with reference standard results 	<ol style="list-style-type: none"> 1. Blind outcome assessment <p>(Objective outcome criteria applied in a "blind" fashion)</p>
I	<ol style="list-style-type: none"> 1. Intention To Treat Analysis (ITT) <i>End Balanced</i> 	<ol style="list-style-type: none"> 1. Inconsistency (I2) (Heterogeneity) 	<ol style="list-style-type: none"> 1. Index test: Describe it and how it was conducted and interpreted 2. Independent test: Index test is not part of reference test. 	

Table 2: RABI Item Description

Type of reporting bias	Definition
Publication bias	The publication or non-publication of research findings, depending on the nature and direction of the results
Time lag bias	The rapid or delayed publication of research findings, depending on the nature and direction of the results
Multiple (duplicate) publication bias	The multiple or singular publication of research findings, depending on the nature and direction of the results
Location bias	The publication of research findings in journals with different ease of access or levels of indexing in standard databases, depending on the nature and direction of results
Citation bias	The citation or non-citation of research findings, depending on the nature and direction of the results
Language bias	The publication of research findings in a particular language, depending on the nature and direction of the results
Outcome reporting bias	The selective reporting of some outcomes but not others, depending on the nature and direction of the results

trials, those responsible for recruitment may systematically enroll severe or less severe cases to either treatment or control groups which will violate the purpose of randomization and the study will be biased. There are ways to ensure proper allocation of patients such as central randomization, in which the individual recruiting the patient makes a call

to a methods center to discover the arm of the study to which the patient is assigned[1, 7, 8], use of opaque envelopes where the envelopes are sequentially numbered or by on-site computer system with group assignments in a locked file.

Attrition bias:

All patients who entered the study

should be accounted for at its conclusion. If this is not done, or if substantial numbers of patients are reported as “drop-out” an attrition bias is considered. The greater number of drop-outs, the more the bias of the trial, because patients who are lost often have different prognoses from those who are retained. Patients who are lost may

be worse or better than those who are not.

At the end of trial, outcome assessment should include each patient with respect to the target outcome. The greater the number of patients whose outcome is unknown (patients lost to follow-up) the more a study's validity is potentially compromised [6, 7, 17].

To assess whether loss to follow up is excessive or not, one can apply the sensitivity analysis, in positive trials consider worst case scenario for the intervention arm, all patients who were lost to follow up did badly, while all lost to follow up in the control arm did well, and then recalculate. If the conclusions of the trial do not change, then the loss to follow-up was not excessive. If the conclusions change, the strength of inference is weakened (that is, less confidence can be placed in the study results)[6, 7, 17].

B (Balanced groups and “Blinding and three Cs”)

Balanced groups:

The purpose of randomization is to produce 2 balanced groups in reference to prognostic factors. Patients' characteristics of the 2 groups are distributed equally.

Blinding and Three Cs:

When the intervention begins, study personnel should remain unaware of whether patients are receiving the experimental therapy or control therapy, including clinicians, patients, data collectors, outcome assessor, data analyzers and any study personnel who are dealing with the patient or his/her data. Study personnel who know that they are on an experimental treatment, who are measuring responses to therapy are likely to have an opinion about its efficacy. These opinions, whether pessimistic or optimistic, can systematically distort the reporting of treatment outcomes, thereby reducing our confidence in the study's results. In addition, unblinded study personnel who are measuring outcomes may provide

different interpretations of marginal findings [7, 18]. Clinicians if unblinded may provide extra care to the experimental group (co-intervention) which may lead to bias. Effective blinding eliminates the possibility of either conscious or unconscious differential administration of effective interventions to treatment and control groups [6, 7]. Blinding maintains the treatment groups' balance. Co-intervention is addition of treatment or procedure outside the study protocol. Contamination is the use of part or all of the treatment or procedure of the other group. Compliance is the adherence of all subjects to the assigned medication.

(Intention to treat analysis)

Patients are analyzed in the groups to which they were randomized. This type of analysis preserves the value of randomization; the two groups will end balanced. Investigators can undermine randomization if they omit from the analysis patients who do not receive their assigned treatment [6, 7].

RABI for validity appraisal of an article about Systematic Review of Therapy:

Seven terms are included in (RABI), Representative sample (cRiteria), Reproducibility, Articles 3S (Search, Selection and Summery), Blind quality assessment, and Inconsistency (heterogeneity).

R (Representative sample and Reproducibility)

Criteria of including and excluding subjects and articles; criteria I means the inclusion and exclusion criteria, the study design, type of patients (age, sex and comorbidity), intervention (type, dose and route), control (placebo, comparator or no control) and outcome (should be clearly defined). PICOT (PICO was explained earlier, but (S) stands for study design [19, 20].

Reproducibility:

Two blinded (independent) reviewers should do the quality assessment [19].

A (Articles 3S “Search, Selection & Summary)

Comprehensive search is to find out all trials that address the same question. Electronic search should include at least the three major databases, Medline (PubMed), Embase and Cochrane central clinical trials registry. Additional electronic search should include other specialized databases according to the question (e.g. for nursing question, Cinahl should be searched as well). Authors then apply the inclusion and exclusion criteria to select the studies that fulfill the inclusion criteria. Authors then summarize (abstract or extract) the selected articles to make the data feasible. Two authors independently should do the selection and abstraction[19]. Authors should include in the search strategy English and non English studies, published and non published, look at the references, contact experts and pharmaceutical companies, do hand search and search www.clinicaltrialregistry.com[19]. The selection of articles according to inclusion and exclusion criteria is to start scanning titles and abstracts then full text, then the summary which is the (abstraction /extraction) of the data from the included studies.

B (Blind quality assessment)

Each selected study needs to be appraised according to the 5 items discussed above in therapy. There are more than 25 appraisal scales available, but the most used are Jadad score and Cochrane Risk of bias (ROB)[19].

I (Inconsistency “heterogeneity”)

When there is inconsistency among the overview results, heterogeneity exists. There are many causes for heterogeneity. Overview may include studies with different patients (age and sex), different interventions (different classes, doses, or route), different outcome definitions, and different study methods. Heterogeneity are best detected by statistical tests (P value and I²)[19].

RABI for validity appraisal of an article about Diagnosis:

RABI covers five important items for validity appraisal of an article about diagnosis, these are: Reference standard, representative spectrum, ascertained (verification), blind comparison of test results and independent (test is not part of reference standard)

R (Reference standard and Representative spectrum)

The new test (index test, test under investigation) should be compared to gold (reference) standard. Reference standard is the one with high sensitivity and specificity, approaching 100% accuracy rate, and experts agree that it is the reference standard[21].

The included sample should be representative, (i.e. includes appropriate spectrum of patients and severity of the condition). Usually tests do better when the disease is severe or in late stage[21]. For example, carcinoembryonic antigen (CEA) is negative in early stage cancer colon but positive in advanced cases. The setting where the study is conducted is important, because cases from primary care are expected to be in the early stage of illness.

A (Ascertained, verification bias)

Results of the new test need to be verified by the results of reference standard. When the new test classifies patients as positive or negative, then the question is raised: Are test results true positive or false positive and for negative results, are they true negative or false negative? All patients have to perform both tests to verify the results of the new test[21].

B (Blind comparison)

Those who evaluate the new test results have to be unaware (blind) of the results of the reference standard, so that they will not be affected (biased) by the results of reference standard[21].

I (Index test and Independent)

Index test:

What is the index test, describe it and interpret the result.

Independent

Index test is independent from reference test:

The new test should not be part of the reference standard. For example in children with urinary tract infection, if the new test is the “urine clarity” and the reference standard is the “urine analysis” there is possibility of bias, as urine clarity is part of urine analysis which will underestimate or overestimate the result[21].

RABI for validity appraisal of an article about Prognosis

RABI covers five important items for validity appraisal of an article about Prognosis, these are: Representative sample, homogeneous cases, attrition (length of follow up and lost to follow up), adjustment of prognostic factors, blind assessment of outcome (objective outcome)

R (Representative sample: setting and similar point)

The setting from where sample is selected is crucial. Tertiary centers with specialized clinics often care for patients with increased illness severity. Research describing the outcomes of patients in these centers may not be applicable to the general patient with the disorder in the community (sometimes referred to as referral bias). Unrepresentative sample is one which is systematically different from the population of interest;[22] an example of this “referral filter bias”, the likelihood of a subsequent non-febrile seizure in children with their first febrile seizure was much lower in community-based populations than in those drawn from hospitals.

Patients included in the study should be at a similar point of the disease process. The point in the clinical course needs not be early, but it does need to be consistent. Patients need to be homogeneous with regard to the stage of disease[22].

A (Adjustment and attrition)

Adjustment: All important prognostic factors should be considered, and the prognosis for each one needs to be calculated separately and in relation to others[22].

Attrition:

A Patient who is lost to follow up may be different from those who are retained, as the number of patients who do not return for follow-up increases, the likelihood of bias also increases. How many is too many? This depends on the relationship between the proportion of patients who are lost and the proportion of patients who have had the adverse outcome of interest. The larger the number of patients whose fate is unknown relative to the number who have had the adverse event, the greater the threat to the study’s validity. Sensitivity analysis will be applied to lost to follow up to determine the size and effect of drop out. Consider that the lost to follow up all develop an adverse effect, add them to the adverse outcome of the study and recalculate[22].

B (Blind assessment of an objective outcome)

There are three types of outcome: Objective one (death), Subjective outcome (Quality of life) and in between Objective/subjective which needs some judgment (Myocardial diagnosis). The more objective is the outcome, the better the assessment[22].

Outcome assessors should be blind to the prognostic factors of patients to minimize bias as much as we can. Age and sex cannot be blinded but other factors can be, like co-morbidity[22].

217 out 243 candidates (89.3%) who attended the workshops have used RABI for at least one article and agreed to join the evaluation study. 187 (86.2%) of them were physicians (different specialties and posts), 19 (8.8%) were nurses and 11 (5.0%) were pharmacists.

217 (100.0%) participants completed RABI for therapy articles, 194 (89.4%) completed it for systematic

Results of Quantitative evaluation of RABI:

	R		A		B		I		P value
	No.	%	No.	%	No.	%	No.	%	
For therapy									
Good and above	201	92.6	194	89.4	176	81.1	205	90.4	0.279
Fair	13	6.0	15	7.0	27	12.4	10	4.6	
Poor	3	1.4	8	3.6	14	6.5	2	0.9	
Total	217	100	217	100	217	100	217	100	
For systematic Review									
Good and above	167	86.0	174	89.7	157	80.9	183	94.3	0.172
Fair	16	8.4	13	6.7	23	11.9	7	3.6	
Poor	11	5.6	7	3.6	14	7.2	4	2.1	
Total	194	100	194	100	194	100	194	100	
For diagnosis									
Good and above	151	87.4	165	95.4	158	91.3	163	88.4	0.365
Fair	14	8.1	8	4.6	9	5.2	10	5.8	
Poor	6	3.5	0	00.0	6	3.5	0	00.0	
Total	173	100	173	100	173	100	173	100	
For prognosis									
Good and above	156	92.8	151	89.9	162	96.4			0.253
Fair	9	5.3	12	7.1	4	2.4			
Poor	3	1.9	5	3.0	2	1.2			
Total	168	100	168	100	168	100			

Table 3: Participants rating for RABI Item's included

	R		A		B		I		P value
	No.	%	No.	%	No.	%	No.	%	
Sequence of Therapy									
Good and above	184	84.8	197	90.8	189	87.1	197	90.8	0.138
Fair	23	10.6	12	5.5	17	7.8	14	6.4	
Poor	10	4.6	8	3.7	11	5.1	6	2.8	
Total	217	100	217	100	217	100	217	100	
Sequence of systematic Review									
Good and above	178	91.8	183	94.3	186	95.9	189	97.4	0.216
Fair	9	4.6	7	3.6	8	4.1	5	2.6	
Poor	7	3.6	4	2.1	0	00.0	0	00.0	
Total	194	100	194	100	194	100	194	100	
Sequence of diagnosis									
Good and above	164	94.8	160	92.5	154	89.0	168	97.1	0.365
Fair	7	4.0	8	4.6	13	7.5	5	2.9	
Poor	2	1.2	5	2.9	6	3.5	0	00.0	
Total	173	100	173	100	173	100	173	100	
Sequence of prognosis									
Good and above	153	91.1	159	94.6	149	88.7			0.245
Fair	11	6.5	7	4.2	13	7.7			
Poor	4	2.4	2	1.2	6	3.6			
Total	168	100	168	100	168	100			

Table 4: Participants rating for RABI Item's Sequence

review, 173 (79.7%) for diagnosis and 168 (77.4%) for prognosis.

Table 3 (previous page) shows the participants' ratings about the items included in RABI. All participants (100%) rated (R) as good and above for all types of articles except prognosis, where 87.5% rated it as good and above. 100% of participants rated (A) as good and above except for therapy and prognosis (90.0 and 87.5% respectively). For (B), all participants rated therapy and diagnosis as good and above while 87.5% rated systematic review and prognosis as good and above. (I) was rated as good and above by all participants except for diagnosis (92.9%). There was no statistical significance of the above mentioned results.

Table 4 (previous page) shows the participants' response regarding the item's sequence of RABI. 84.8%, 91.8%, 94.8% and 91.1% of participants rated (R) as good and above for therapy, systematic review, diagnosis and prognosis, respectively. For (A), 90.8%, 94.3%, 92.5% and 94.6% of participants rated it as good and above. For (B), 87.1, 95.9, 89.0 and 88.7% of participants rated it as good and above, for therapy, systematic review, diagnosis and prognosis respectively. Lastly, 90.8%, 97.4% and 97.1% of participants respectively rated (I) as good and above for therapy, systematic review and diagnosis respectively (there is no (I) for prognosis).

In comparison with user's guide worksheets in general terms, 100.0% of participants considered RABI a user friendly tool; 76.9% reported that it is easy to memorize and recall, 81.8% believe that RABI would replace the usual worksheets for validity appraisal and finally 100.0% would recommend others to use it.

How to use RABI:

RABI is a user friendly (4 X 4) table that is easy to remember and recall. The candidate decides what type of article he is going to appraise (therapy, systematic review, diagnosis or prognosis), then, he

starts to follow the letters of RABI one by one and its corresponding explanation in line with the article type.

Discussion

EBM is integrated into undergraduate medical curriculum [27-30] and residency programs [31-34] such as Family Medicine, Pediatrics, Internal Medicine and Obstetrics and Gynecology in many medical schools and programs. King Saud bin Abdulaziz University for Health Sciences (KSAU-HS) EBM curriculum for undergraduate medical college was described elsewhere [35, 36], and the core content of the EBM curriculum is critical appraisal of articles.

RABI is aimed at the medical students, residents and fellows who are preparing for examination and need to remember and recall all items to answer validity questions.

Twenty four items were generated from User's guide to medical literature [4, 7-11], Centre for Evidence Based Medicine critical appraisal sheets [12], Cochrane Risk of Bias (ROB) tool [13, 22], and Quadas 2 tool [14, 37, 38].

Critical appraisal assessment examinations have different formats such as OSCE [31], computer based OSCE [39, 40], self-assessment instrument [41, 42], best evidence medical education (BEME) guidance self-assessment [43], portfolio [32], performance-based assessment [44, 45], scenario-based user testing [46], and pre and post assessment based on appraisal worksheets [47, 48].

RABI is probably needed for all the above exam formats.

RABI was rated high compared to user's guide worksheets for items included and their sequence.

Conclusion

RABI is an acronym, four-in-one validity assessment, easy to teach, and easy to remember and recall tool.

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A new treatment approach in tuberculosis

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Introduction

Tuberculosis (TB) is a common, chronic, and recurrent infectious disease caused by various strains of mycobacteria, usually *Mycobacterium tuberculosis* (MTB). Because MTB retains certain stains even after being treated with acidic solution, it is classified as an acid-fast bacillus (1). TB is the most common cause of infection-related death worldwide and the sixth most important cause of death overall (2). Although it can infect any part of the body, lungs are the most frequently affected organs. The upper lobes of lungs are more frequently affected by unknown reasons as yet. It may be due either to better air flow or to poor lymphatic drainage of the upper lobes. It is spread by the air when patients with an active infection cough or sneeze. Most infections are asymptomatic and latent, but about one in ten latent infections eventually progresses to the active disease. The common symptoms of active infection are chronic cough, fever, night sweats, and weight loss. The World Health Organization estimated that there was about one third of the world population infected, and there were an estimated 8.8 million incident cases, mostly occurring in Asia (59%) and Africa (26%) in 2010 (3). Tuberculin skin test is positive in about 80% of the population of many Asian and African countries whereas only in 5-10% of the population of the United States (3). More people in the developing world get the disease because of compromised immunity, largely due to high rates of human immunodeficiency virus (HIV) infection (4). The infection may spread outside the respiratory organs; that is called extrapulmonary TB, and it occurs more frequently in immunosuppressed individuals. In those with HIV, extrapulmonary TB develops in more than 50% of cases (5-7). Significant extrapulmonary sites include the pleura, central nervous system, lymphatic system, genitourinary system, bones, and

Abstract

Role of total excision of lymphadenopathies (LAPs) if they are limited in number is unknown in the treatment of tuberculosis (TB). A 14-year old male applied with weight loss. On physical examination, there were multiple right axillary LAPs with sizes of 3x2 cm. In laboratory examination, C-reactive protein (CRP) was 2.1 mg/dL, erythrocyte sedimentation rate (ESR) was 73 mm/hr, and lactate dehydrogenase (LDH) was 250 IU/L. Tuberculin skin test showed a 22 mm of induration. The right axillary LAPs were excised, totally, and histological examination demonstrated granulomas with Langhans-type giant histiocytes. After the operation, ESR, CRP, and LDH values and his weight returned to normal without any treatment. Secondly, a 43-year old female applied with fever, night sweats, and weight loss. On physical examination, there were multiple and conglomerated left axillary LAPs with sizes of 6x4 cm. In laboratory examination, CRP was 5.2 mg/dL, ESR was 74

mm/hr, and LDH was 329 IU/L. Tuberculin skin test showed a 20 mm of induration. The LAPs were excised, totally, and histological examination demonstrated granulomatous lymphadenitis with epithelioid histiocytes, Langhans-type giant cells, and caseified necrosis. After the operation, fever and night sweats disappeared, and CRP, ESR, and LDH values were normalized. She returned to normal weight within two months without any antituberculous treatment. As a conclusion, total excision of LAPs if they are limited in number may both have a diagnostic and curative role in TB, probably by decreasing large numbers of bacteria, so remaining small numbers can be eliminated by immune system, alone.

Key words: Tuberculosis, total lymph node excision

joints. Role of total excision of lymphadenopathies (LAPs) if they are limited in number, is unknown in the treatment of TB.

First Case

A 14-year old male patient applied to the Internal Medicine Polyclinic of the Mustafa Kemal University with the complaint of weight loss, and he lost 4 kg during the last two months. He did not have any significant health problems before, and there was nothing significant in his family history about health. In his physical examination, there were multiple and conglomerated right axillary LAPs with maximal sizes of 3x2 cm for each. They were hard and slightly painful in examination. He initially observed them one month ago, but they increased in size over time. In laboratory examination, C-reactive protein (CRP) was 2.1 mg/dL, erythrocyte sedimentation rate (ESR) was 73 mm/hr, lactate dehydrogenase (LDH) was 250 IU/L, and immunoglobulin G was 1.730 mg/dL as abnormal findings. His posterior-anterior (PA) chest X-ray was normal. Tuberculin skin test showed a 22 mm of induration. There were a few small (less than 1 cm) LAPs in abdomen in computed tomography (CT) scan. The right axillary LAPs were excised, totally, and histological examination demonstrated granulomas with Langhans-type giant histiocytes. There was not any specific finding in his bone marrow aspiration biopsy. After total excision of the right axillary LAPs, the patient started to feel better himself, and CRP, ESR, and LDH values returned to normal within two weeks. He regained his lost weight in one month. His control CT scan of abdomen was also normal, and he is still on our follow up for the last one year without any antituberculous treatment.

Second Case

A 43-year old female patient applied to the Internal Medicine Polyclinic of the Mustafa Kemal University with the complaints of fever, night sweats, and weight loss during the last two years. She lost 14 kg during the period. She was an immigrant from Afghanistan, and she was

living in Turkey since 1998. In her physical examination, there were multiple and conglomerated left axillary LAPs with sizes of 6x4 cm. They were hard, immobile, and slightly painful on examination. She detected them for the last one year with an increase in size by time. In laboratory examination, CRP was 5.2 mg/dL, ESR was 74 mm/hr, LDH was 329 IU/L, and hematocrit value was 35% as the abnormal results. Tuberculin skin test showed a 20 mm of induration. Her PA chest X-ray was normal. Ultrasonographically, the LAPs were well bordered, hypoechoic, and oval in shape. In her abdominal ultrasonography, grade 1 hepatosteatosis was detected. In CT scans of thorax and abdomen, there was nothing other than hepatosteatosis and left axillary LAPs. There was not any specific result in her bone marrow aspiration biopsy. The LAPs were excised, totally, and histological examination demonstrated granulomatous lymphadenitis with epithelioid histiocytes, Langhans-type giant cells, and caseified necrotic foci. After total excision of the LAPs, fever and night sweats disappeared. CRP, ESR, and LDH values were normalized within two weeks. She returned to previous body weight within two months, and she is under our follow up for the last one year without any antituberculous treatment again.

Discussion

TB is a leading cause of preventable morbidity and mortality worldwide. It remains as a global problem with 8.7 million new cases and 1.4 million deaths in 2011 (8). MTB is the predominant cause in humans, and it was first identified as the causative agent by Robert Koch in 1882. MTB is a small, aerobic, nonmotile bacillus. It can withstand weak disinfectants, and survive in a dry state for weeks. As the world's most successful intracellular pathogen, it can survive inside the macrophages by blocking phagosome maturation and establish chronic infection characterized by granulomas. About 90% of the infected individuals with MTB have asymptomatic and latent infections, with only a 10% of lifetime

chance of activation. Those people with latent infection are thought to be non-contagious. In those with HIV, the risk of developing active TB increases to nearly 10% a year. If effective treatment is not given, the death rate is increased up to 66% in active cases. *Mycobacterium bovis* was once a common cause of TB, but the introduction of pasteurized milk has largely eliminated it as a public health problem in developed countries (9). TB is one of the most devastating diseases of mankind. It is closely linked to overcrowding and malnutrition, so it is defined as one of the major diseases of poorness (4). Immunocompromised individuals have a significantly higher prevalence of TB (10). Other people at high risk include illicit drug users, prisoners, homeless individuals, children in close contact with high-risk people, medically underprivileged and resource-poor communities, and HIV infected cases (2). For example, 13% of all TB cases are infected by HIV, and this is especially a major problem in sub-Saharan Africa (11). Additionally, smokers have nearly twice the risk (12). Alcoholism and diabetes mellitus also increase the risk (4,13). Certain medications such as corticosteroids and infliximab are also becoming important risk factors now (4).

Miliary TB is a pathological name describing millet seed-sized (1-2 mm) granulomas in various organs affected by tubercle bacilli (14). It results from massive lymphohematogenous dissemination from a MTB-laden focus. Males appear to be more frequently affected by miliary TB both in children and adults (15). Miliary TB is mostly fatal within one year if untreated (14). It is characterized by miliary shadows on chest radiography (16). Positron emission tomography-CT is suitable for defining the extent of disease (17). Bacille Calmette-Guérin vaccination has resulted in substantial reduction in miliary TB and TB meningitis in children and young adults. Although miliary TB has been considered to be a childhood disease for a long time (18), it is also increasingly being recognized in adults during the last

decades (19). Two additional peaks are evident nowadays involving adolescents and elderlies (20). Additionally, there is an increase in miliary TB with the HIV epidemic, introduction of biological and immunosuppressive drugs for treatment of various disorders, increasing numbers of organ transplantation, and chronic hemodialysis programs, nowadays (21,22).

Chemotherapy is usually effective if the full course is given. Even strains of tubercle bacilli that are considered susceptible to a drug invariably include a small number that are resistant. Thus, disease may improve at first in response to a single drug but then worsen due to the resistant mutants' divisions. Thus, to prevent development of resistance, clinical TB must always be treated with at least two drugs that act through different mechanisms. Other drugs should be added in inner-city patients where spread of isoniazid-resistant TB is common and cannot be cured with the two most effective drugs. According to our experience, treatment of an active TB should be continued for 12 months at least with three drugs after the initial usage of streptomycin for two months, intramuscularly. Isoniazid is bactericidal, gains ready entrance to body cells and cerebrospinal fluid (CSF), and is highly effective against large populations of extracellular bacilli. It is the single most useful and least expensive drug for TB. It is also safe during pregnancy. Rifampin is bactericidal, well absorbed, penetrates well into cells and CSF, and acts rapidly against the extracellular bacilli. It is also important in eliminating largely dormant organisms in macrophages or caseous lesions that can cause late relapse. Thus, isoniazid and rifampin should be used throughout the course. Streptomycin resistance is still uncommon. It is given by injection five days a week. CSF penetration is poor, but intrathecal administration should not be used if other effective drugs are available. Pyrazinamide is also bactericidal, and now used routinely with isoniazid and rifampin to guard against treatment failure due to

isoniazid resistance. Ethambutol is bacteriostatic that deters resistance to bactericidal drugs.

As the other modes of therapy, surgical resection of a persistent TB cavity may occasionally need to be performed to eliminate the large population of bacteria that have begun to show drug resistance. In patients with adult respiratory distress syndrome, excessive fever, or difficulty in breathing, corticosteroids for 2 to 3 weeks may be lifesaving. Such therapy is also indicated when cerebral edema accompanies tuberculous meningitis. Physiologic doses of a mineralocorticoid are adequate in treating the adrenal insufficiency that accompanies Addison's disease. Corticosteroids that are needed for other indications cause no danger in a patient with active TB who is receiving an effective TB regimen. As also observed in the two study cases, total excision of LAPs if they are limited in number may be another treatment option in TB, probably by decreasing large numbers of bacteria. The remaining small numbers can be eliminated by immune system, alone. This way, we can escape from usage of several drugs for a long period of time and their side effects and costs. This method is also used for many malignancies for several years under the heading of adjuvant therapy. Adjuvant therapy is usually given after surgery when all detectable malignant tissues have been removed, but where there remains a statistical risk of relapse due to occult disease. We did not require any systemic chemotherapy due to normalization of all laboratory and clinical abnormalities of the patients after the total excision of LAPs.

As a conclusion, total excision of LAPs if they are limited in number may both have a diagnostic and curative role in TB, probably by decreasing large numbers of bacteria. The remaining small numbers can be eliminated by immune system, alone. This way, we can escape usage of several drugs for a long period of time and their side effects and costs with a close follow up of the cases.

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Role of herbal medicines in cardiovascular diseases

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Introduction

Cardiovascular diseases, an umbrella term for a number of conditions that affect the heart and the vessels, are one of the major threats to the developing and the developed world. The world is seeing an escalation in heart diseases despite advancements in medicine and research, attributed to factors such as genetic, environmental and life style behaviours. Nevertheless, the significance of medicines, whether allopathic, homeopathic or traditional, cannot be disregarded. From primeval times, traditional medicine has been in place and herbs have been used by people from archaic ages. Today, in this scientific era also, herbal or botanical preparations, commonly referred to as Complementary and Alternate Medicine (CAM), are quite widespread in the West and the East, being available over-the-counter, whereas in some countries, essential oils, herbal extracts, or herbal teas can be found in pharmacies with conventional drugs. CAM encompasses a diverse group of therapies that fall outside the paradigm of conventional medical practice, and are often used in conjunction with or alongside such practices. Complementary Medicine is the use of CAM together with conventional medicine, whereas alternate medicine is using CAM in place of conventional medicine. It will be worthwhile stating that CAM is to be regarded as integrated medicine rather than a separate entity. The different types of CAM used are natural products, mind and body medicine, manipulative and body-based practices(1). The use of CAM is prevalent in the treatment of many chronic and acute conditions including cardiovascular diseases, asthma, infections, prostate problems, depression, inflammation, cancers and to boost the immune system. There is evidence from different countries regarding utilization of various CAM modalities

Abstract

Cardiovascular diseases, an umbrella term for a number of conditions that affect the heart and the vessels, are one of the major threats to the developing and the developed world. The aim of this review is to assess the effects of various herbal components in preventive cardiology. The search engine used was Pubmed and related websites to explore for chemical constituents, physiological actions and drug interactions through studies and review articles encompassing herbal medicines in cardiovascular diseases. This article presents key features of a few commonly used herbs, their modes of action and some interactions with allopathic medications prescribed for cardiovascular disorders. Unfortunately the scientific data on herbal medicine is yet in its infancy and it is of utmost importance to develop more effective, affordable health promotion and treatment. The need and demand for rigorous

scientific examination of herbal medicines is the call of the hour to prove compatibility of these constituents in order to combat this deadly syndrome affecting a vast majority of population.

Key words: Herbal medicines, cardiovascular disease

for disease management in conjunction with conventional medicine(2-4).

Herbal Medicines and Cardiovascular Diseases

Herbal treatments used in cardiovascular diseases are in patients with congestive heart failure, hypertension, angina pectoris, atherosclerosis, cerebral insufficiency, venous insufficiency and arrhythmia. Literature states that herbs and plants are processed, however, the problem of standardization exists, and components are likely to vary significantly(5-6). At the same time, argument to the situation is that the pharmaceutical industry has also had the contribution from herbs in some commercially made preparations. To name a few, ephedrine from *Ephedra sinica* (ma-huang), digoxin from *Digitalis purpurea* (foxglove), salicin (source of aspirin) from *Salix alba* (willow bark) and reserpine from *Rauwolfia serpentina* (snakeroot)(7-8).

In comparison to the conventional medicines, most commonly cited reasons for using traditional medicines are affordability, easy access, less concerns about adverse reactions, patient's ideology satisfied, presumed to be close to natural products, therefore more safe and non-toxic. This is not necessarily true, especially when herbs are taken with prescription drugs, over-the-counter medications, or other herbs, as is common practice(9).

The use of herbs is a time-honoured approach to strengthening the body and treating diseases. Herbal supplements are generally considered harmless, although they contain pharmacologically active ingredients, and may have adverse outcomes in addition to beneficial effects. Moreover, they contain components that can trigger side effects and interact with other herbs, supplements and medication. One article concluded that 15% of patients use herbal medicines in addition to allopathic medicines for cardiovascular diseases. The herb-drug interaction and adverse effects

were mild and not life threatening, yet noticeable(10-11). Another study from Jordan stated 14% of patients presenting to cardiology outpatients consumed different herbal preparations. Hawthorn and ginger were the most commonly used; side effects were observed in a very minute number of patients with hawthorn only(12).

The aim of this review is to assess the effects of various herbal components in preventive cardiology. The search engine used was Pubmed and related websites to explore for chemical constituents, physiological actions and drug interactions through studies and review articles encompassing herbal medicines in cardiovascular diseases. This article presents key features of a few commonly used herbs, their modes of action and some interactions with allopathic medications prescribed for cardiovascular disorders.

Hawthorn (*Crataegus* Species)

Hawthorn is remembered by its Latin names, *Crataegus laevigata*, *Crataegus oxyacantha*, *Crataegus monogyna*, commonly known as Mayhaw and Thornapple. It is a spiny flowering shrub of the rose family, including a number of species which are medicinally used for treatment of various ailments, particularly angina, heart failure and hyperlipidemia(13). The leaves, fruits and flowers of *Crataegus* species contain biologically active ingredients which are oligomeric substances such as procyanins, flavonoids, and catechins(14). The extracts from various active constituents are said to have antioxidant properties and supposed to inhibit the formation of thromboxane(15). A couple of studies in isolated perfused hearts have shown there is cardioprotective effects without affecting coronary blood flow; in addition there is evidence that simultaneous positive cardiac inotropic and vasodilator actions(16-17). Another proposed mechanism of action of flavonoids is the inhibition of 3',5'-cyclic adenosine monophosphate

phosphodiesterase from this herb(18). Nonetheless, it is also suggested to be careful while using this herb with cardiac glycosides, whose activity is enhanced, due to its lower arrhythmogenic risk(5). Literature evidence for supporting interaction between hawthorn and digoxin is dual; one study stated these can be co-administered safely, whereas the more recent study claimed patients on digoxin should avoid hawthorn(19-20).

Garlic (*Allium sativum*)

Central Asia seeds the origination of garlic centuries back and since then it has been since used as flavouring agent, traditional medicine, and a functional food(21). Its role in the inhibition of pathogenesis of cardiovascular diseases, chronic diseases associated with aging and in the prevention of cancer has been discussed in one of the studies(22). There have been various theories regarding the mode of action of garlic and its constituents. The intact cells of garlic bulbs contain an odorless sulfur-containing amino acid, allinin. Once garlic is crushed, allinin is converted into allicin by an enzyme allinase. Authorities now agree that allicin and its derivatives are the bioactive constituents of garlic(5). Allinin is supposed to have strong antibacterial properties, that are also unstable and odourificous. The self-condensation products of allicin, Ajeones are said to have antithrombotic action, in addition to its potential effect in the inhibition of platelet aggregation(23). Dissolution of clots and thrombi through fibrinolysis is also improved by garlic. In vitro studies have verified that aged garlic extract, a modified raw form of garlic, improves circulation and blood properties by preventing lipid peroxidation and hemolysis in oxidized erythrocytes(24). A couple of case reports have published the adverse effects of garlic ingestion, where one claimed allergic dermatitis observed in a patient taking raw garlic(25). Another stated that the antithrombotic activity of garlic might interact with oral anticoagulants; therefore, caution must be exercised(26).

Ginger (*Zingiber officinale*)

Ginger is a knotted, thick, beige underground stem, called a rhizome. It is one of the best known spices worldwide for more than 2000 years and it has been used medicinally in Asian, Chinese and Arabic cultures. The main biologically active ingredients in ginger, namely gingerols, shogaols, paradols, and volatile constituents like sesquiterpenes and monoterpenes are mainly attributed to the health-enhancing perspectives of ginger(27). Studies have proven its lipid lowering effect, thereby preventing blood clots, and thus preventing atherosclerosis(28). In vitro study has shown effects of dried ginger powder in reducing cholesterol, though not to a significant level, yet, noticeable(29). It has also been shown to decrease blood pressure through a dual inhibitory effect via blockade of calcium ion channels and via stimulation of muscarinic receptors(30). Drug interactions are rare but care should be taken when consuming with anti-coagulants, like warfarin and aspirin. In addition, there might be possible interactions with anti-hypertensive drugs. One case report evidenced interaction between an oral anticoagulant (phenprocoumon) and ginger, resulting in elevation of INR and epistaxis(31).

Ginkgo biloba (*Pterophyllus salisburiensis*, *Salisburia adiantifolias*)

Ginkgo biloba, remembered by famous names as Maidenhair tree, Fossil tree and Kew tree, is one of the oldest living tree species, where a single species can live as long as 1,000 years and grow to a height of 120 feet. They are sturdy trees planted across urban areas in the United States. It has fan-shaped leaves and inedible fruits that produce a strong odour with small branches. There are about more than 40 substances in Ginkgo tree but only two of them have been found to be significant. One is Flavonoids; these are plant derived antioxidants that help to decrease the capillary permeability and fragility and are free-radical scavengers. The other

one is Terpenoids (i.e., ginkgolides) which inhibit platelet-activating factors that help to decrease vascular resistance, improving circulatory flow without disturbing the blood pressure(32). There are controversial results regarding effects of G biloba on the cardiovascular system. Studies have suggested antioxidant and free radical scavenger effects, inhibition of platelet aggregation, and association of bleeding with G biloba, which has been attributed to antiplatelet aggregation effects. It has also been suggested that G biloba improved blood flow by increased release of nitric oxide and the inhibition of nitric oxide degradation in the endothelium(33-35). Another study failed to find out any evidence regarding G biloba in reducing total or CVD mortality or CVD events, although few peripheral vascular disease events occurred in the placebo arm(36). One study revealed that G biloba extracts exerts cardioprotective effects reducing ischemia-caused impairment of functions of heart mitochondria. It is supposed that free radical-induced myocardial damage and impairment of vascular endothelium-dependent relaxation are amongst the most important mechanisms responsible for ischemic heart injury(37). This is a notorious herb because of its interactions with prescription and the non-prescription drugs. Few drug interactions worth mentioning are with antidepressants and antihypertensives(38). Ginkgo might raise the risk of bleeding, especially if it is taken with blood-thinners such as warfarin (Coumadin), clopidogrel (Plavix), and aspirin(38-39). There has been bleeding in the brain reported when using a ginkgo product and ibuprofen(40). Interactions between cyclosporine and ginkgo or onion have been reported; it was indicated that ginkgo and onion markedly decreases the oral bioavailability of cyclosporine(41).

Ginseng (*Panax Species*)

The medical implications of this herb in East Asian countries have been proven for thousands of years as an adaptogen and a tonic. The major bioactive components of *Panax*

ginseng are the ginsenosides, a group of saponins. Ginseng also contains several valuable nonsaponin components, including essential oils, antioxidants, polyacetylenic alcohols, peptides, amino acids, polysaccharides, and vitamins. The two species that have been the most extensively researched are *Panax ginseng* (Asian ginseng) and *Panax quinquefolius* (American ginseng)(42). So far, the use of ginseng for the treatment of CVD is under research. One hypothesis postulated that it helps in hemostasis and the treatment of patients with angina and CAD, by acting on the calcium ion channel antagonist in vascular tissues, resulting in lowering of blood pressure(5, 43). Yet, another study suggested that saponins inhibit atherogenesis by interfering with the proliferation of smooth muscle cells(44). Studies demonstrated that *P. notoginseng* might be useful as an antianginal drug, due to its activity in dilatation of coronary arteries in all concentrations(45-46). Regarding hypertension, this herb causes increased endothelial-dependent vessel dilatation, it could be considered for regulation of blood pressure(47). Among the drug interactions, one of the possible drugs to look out for while taking ginseng is anti-coagulants, especially warfarin(48).

Foxglove (*Digitalis purpurea/lanata*)

The different names by which this herb is well-known are Witches' Gloves, Dead Men's Bells, Fairy's Glove, Gloves of Our Lady, Bloody Fingers, Virgin's Glove, Fairy Caps, Folk's Glove and Fairy Thimbles. The normal life of a foxglove plant is biennial; leaves form a rosette close to the ground during the first year, succeeded by a spike with blooms in the second year. Plant taxonomy classifies foxglove flowers as *Digitalis purpurea*(49). *Digitalis*, commercially known as cardiac glycosides, contains four important glycosides of which three are cardiac stimulants. The most powerful is Digitoxin, an extremely poisonous and cumulative drug, water insoluble; Digitalin, crystalline and also water insoluble; Digitein, amorphous, but readily

water soluble; Digitonin, a cardiac depressant, containing none of the physiological action peculiar to Digitalis, and is identical with Saponin, the chief constituent of Senega root(50). Digitalis preparations increase cardiac contractility (positive inotrope) and act as an antiarrhythmic agent to control heart rate. The mechanism underlying these actions of digitalis compounds is believed to be brought about by increased availability of calcium ions in heart cells and increase in intracellular calcium ion activity(51). The low therapeutic index of digoxin makes patients highly vulnerable to toxicity producing a toxidrome characterized by gastrointestinal, neurologic, electrolyte, and nonspecific cardiac manifestations(52).

Conclusion

Complementary and Alternate Medicine (CAM), which is referred to array the plethora of "non-conventional health practices", presents a challenge to the medical community and opportunities exist for policy and research in the health care system(1). A remarkable number of people seek traditional remedies that have lead to vast achievements and dramatic successes in the field of unconventional medicine.

Conversely, pertinent literature indicates that the available clinical evidence in this regard is still inadequate and sometimes inconclusive. It might be assumed that the active components in herbal medicines are diluted resulting in fewer adverse effects, in comparison with the concentration of active components in the allopathic medicines. Nonetheless, even a small margin of error in cardiovascular diseases, a serious health hazard, is unacceptable, and no herbal remedy should be initiated without careful considerations.

Unfortunately the scientific data on herbal medicine is yet in its infancy and it is of utmost importance to develop more effective, affordable health promotion and treatment. The need and demand for rigorous scientific examination of herbal

medicines is the call of the hour to prove compatibility of these constituents in order to combat this deadly syndrome affecting a vast majority of population.

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CME Case



Mr Butt is a 58 year old labourer whom you have been managing for almost twenty years . For most of that time you have found him to be hypertensive and despite your best efforts his BP control has been 'sub-optimal'.

His most recent BP has been 155/95mmHg despite being on two agents.

Mr Butt has also been a smoker but you did convince him to stop about five years ago. He has also required a 'statin' for cholesterol in recent years.

Mr Butt comes in requesting a 'thorough going over' as his brother has recently died from an AMI. You decide to check his renal function amongst his investigations and to your surprise his serum creatinine is 210 $\mu\text{mol/l}$ (normal <120 $\mu\text{mol/l}$)

You have no record of a previous level.

You decide to follow this up with some further tests.

Question 1

Which of the following would be useful?

1. MSU for quantitative urine microscopy, culture and sensitivity
2. 24 hour urine creatinine
3. Urine dipstick
4. ECG
5. Autoantibody screen
6. A repeat U&E's Cr

Author's Answer:

MSU, Urine dipstick, ECG, A repeat U&E's, Cr

(See page 45 for feedback)

Further history

You determine that Mr Butt has stable renal impairment, with a serum creatinine on repeat testing of 205 mmol/l. A dipstick showed only +1 protein and no blood and a follow-up MSU with urine microscopy, culture and sensitivity was unremarkable. The ECG showed some lateral T wave inversion consistent with 'ischaemia or a strain pattern'.

Question 2

You decide to image his kidneys. Which ONE of the following is the best test?

1. Renal ultrasound
2. IVP
3. CT scan
4. Nuclear scanning
5. Renal ultrasound and Doppler.

Author's Answer:

Renal ultrasound

Ultrasound is probably the best test in this circumstance. It provides an assessment of renal size, as most causes of chronic renal failure are associated with small kidneys - the exception being polycystic kidneys and sometimes diabetes. Ultrasound also excludes (or diagnoses) obstruction very well. Obstruction is important in this setting as even late relief of obstruction may result in significant improvement in renal function. Scars, for example from past reflux nephropathy, can often be seen. Ultrasound does not provide any functional assessment but also is not interfered with by poor renal function and is non-invasive.

Further history

The kidneys are a little small (right 9.5 cm, left 9 cm) but there is no abnormality found. It appears likely that Mr Butt has chronic renal impairment with no reversible component. A Nephrologist feels that he has advanced nephrosclerosis (the not so benign end of the spectrum of benign nephrosclerosis) as a result of his long history of hypertension and other vascular risk factors. He has been advised that his kidneys will likely continue to deteriorate over the next 3-6 years at which point he will probably need dialysis.

Question 3

What are the factors that will influence the rate of progression of his renal impairment over the next few years?

Select one only.

1. A strict low-protein diet
2. Total avoidance of salt
3. Tight blood pressure control
4. Absolute requirement for an ACE-inhibitor
5. Maintaining a low cholesterol

Author's answer**Tight blood pressure control.**

There is no question that tight blood pressure control is very important. It has been known for some time that the rate of progression of renal failure due to most renal disease is slowed by blood pressure control. Recent trials have confirmed this and suggested even tighter margins with lower target blood pressures. Target levels below 130/80 mmHg, and below 125/75 mmHg if 1 g daily or proteinuria is present, should be kept in mind.

Feedback on other (incorrect) choices in Question 3:**A strict low-protein diet.**

Low-protein diets have been through several phases. Low protein diets certainly reduce the symptoms of more advanced renal failure (or more specifically "uraemia") but will not have such a benefit for Mr Butt. The average 'wedstern' diet contains 1-1.5 gm/kg of protein per day. Restricting this to about 0.7 g/kg/day may well help slow the rate of progression of his renal failure. However a prolonged period of time on a low-protein diet, especially if not closely supervised, may result in some degree of malnutrition and thus moderate protein restriction only is usually recommended (e.g. 0.8g/kg/day). With more advanced renal impairment, patients often auto-restrict their protein intake via a loss of appetite.

Total avoidance of salt.

Avoidance of salt is a useful adjunct to BP control. How far do you go? Patients should be warned that it takes at least 4-6 weeks to become accustomed to a very low salt diet. If this is tolerated, well and good, but many patients end up eating very little under this restriction and are probably better off eating some salt. It should also be remembered that some renal conditions result in salt (and water) wasting, especially predominantly tubular disorders such as analgesic nephropathy and reflux nephropathy (whereas the glomerular disorders tend to retain salt and water). A diuretic may be an alternative to a low salt diet. Diuretic therapy will be more effective if a low salt diet is followed.

Absolute requirement for an ARB or ACE-inhibitor.

ARBs and ACE-inhibitors appear to offer benefit over and above simple blood pressure control, compared to other antihypertensive agents. Having said this, some recent trials have suggested that if blood pressure control is tight then the differences are less and that other antihypertensive agents (especially beta-blockers) may offer near equal benefits. Most nephrologists currently prefer to use ARBs or ACE-inhibitors as a first choice but accept other agents as good alternatives if these agents can't be used (e.g. due to renal artery stenosis, rising creatinine, hyperkalaemia, drug reactions, cough for ACEi).

Maintaining low cholesterol.

Maintaining a low cholesterol is probably beneficial. This issue has not been addressed in a large scale manner specifically in terms of rate of progression of renal failure. However we know that progression is at least in part related to intra renal haemodynamics and the state of the intra-renal vasculature. Diminishing any deterioration in the state of these vessels will be helpful and so the nephrologists have 'borrowed' these concepts from the cardiologists. Exact target levels have not been defined in patients with renal impairment, but prudence suggests that a total cholesterol below 4.0mmol/L and LDL-cholesterol < 2.5 mmol/L would be wise. The Heart Protection Study included subjects with serum creatinine levels up to 200 mmol/L and equivalent cardiovascular benefits were seen independently of renal function.

END OF CASE

Once on dialysis, Mr Butt has a mortality rate of about 13-16% per year (or about 15-20 deaths per 100 patient years). This figure is much higher if he happens to have diabetes.

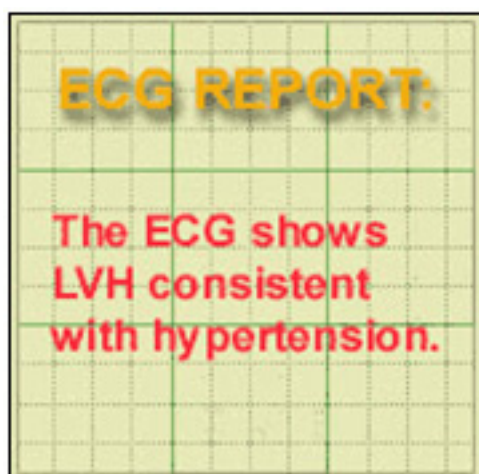
Question 1 feedback:

MSU (Mid Stream Urine sample) for quantitative urine microscopy, culture and sensitivity

An MSU would be quite useful. In the circumstance of newly discovered renal impairment it is important to determine whether there is evidence for glomerulonephritis, (GN) and whether there is likely to be an acute aggressive form of glomerulonephritis. GN remains the most common cause of renal failure in Australia. If there are no (glomerular) red cells in the urine, then rapidly progressive GN would be unlikely. Most forms of severe GN exhibit high numbers of glomerular red cells in the urine, often with red cell casts.

ECG

An ECG may actually be quite useful. Mr Butt is a likely candidate for vascular disease (family history, smoker, cholesterol, hypertension) and the presence of silent ischaemic heart disease may be a clue to renovascular disease. This is usually a small vessel problem within the kidney, manifest as slowly progressive renal failure without urinary protein or red cells, usually with hypertension and other vascular disease. It is different from large vessel 'renal artery stenosis'.

ECG report.**A repeat Urea & Electrolytes and Creatinine**

A repeat U&E's, Cr is useful, especially to determine whether there is deteriorating renal function or whether the serum creatinine is stable at its current level. The electrolytes may give a hint as hyperkalaemia is more common with acute deterioration and renal artery stenosis may cause hyperkalaemia. There is always the chance that the initial result is a 'lab error' but this is grasping at straws!

Urine dipstick

A urine dipstick will quickly tell you whether there is significant proteinuria or haematuria. Many forms of renal disease will exhibit some proteinuria, however, advanced nephrosclerosis (which Mr Butt may have) may only have low grade proteinuria, e.g. +1 only on dipstick.

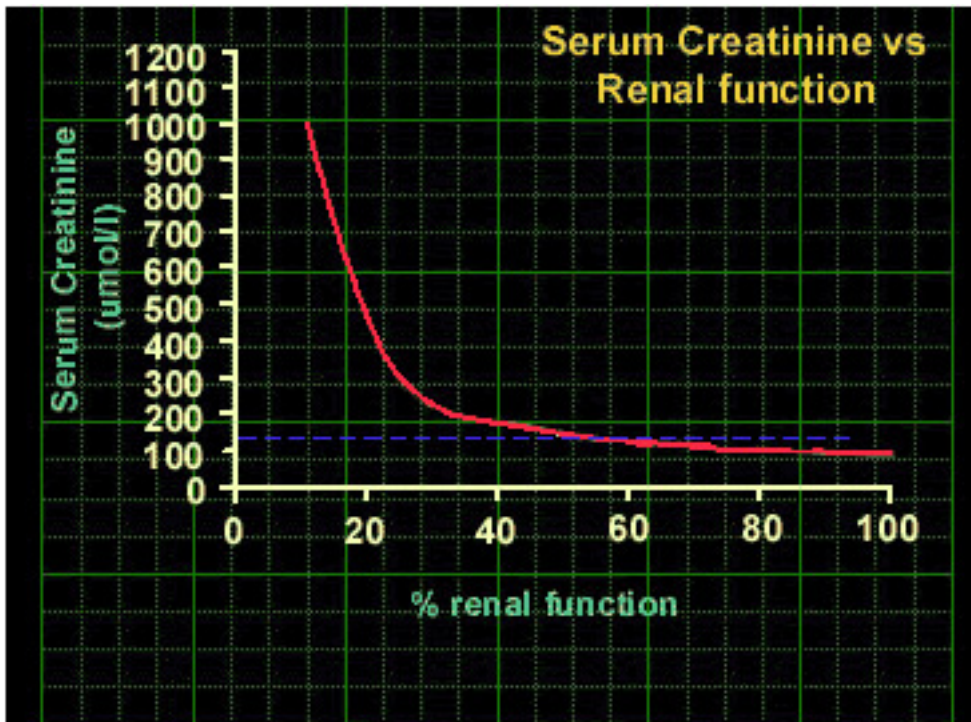
Autoantibody screen

An autoantibody screen would not be particularly useful as most auto-immune diseases are uncommon at this age. There is one particular auto-immune disease which is relatively common in this setting, this being small vessel vasculitis also called microscopic polyangiitis. This could be the case with Mr Butt if there were red cells in the urine. A specific antibody test needs to be ordered (ANCA antibodies) and this is not usually included in the standard "autoantibody screen".

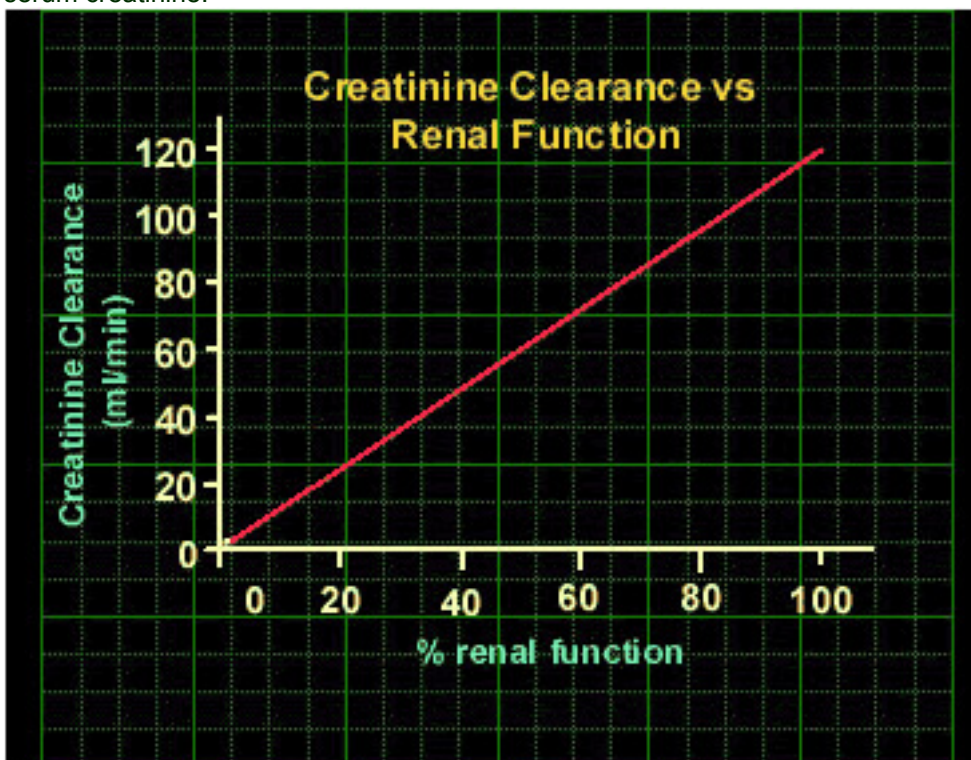
24 hour urine creatinine

A 24 hour urine creatinine falls short of the mark! Whenever ordering a 24 hour urine, request 'creatinine clearance' and not just 'creatinine'. The latter will only give the creatinine excretion, which is relatively unhelpful. A creatinine clearance (which requires a synchronous blood creatinine level) will provide details

of the renal function, at least in terms of the glomerular filtration rate. A well muscled man of 66 would be expected to have a creatinine clearance (CrCl) of one third of normal or less with a serum creatinine of 210 $\mu\text{mol/l}$. A CrCl is a far better way of documenting the renal function in mild renal impairment than a single serum creatinine as it changes in a linear fashion with the changing renal function.



Non linear relationship of serum creatinine level to renal function. The dotted line indicates the upper limit of normal serum creatinine.



Linear relationship between creatinine clearance and renal function.

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