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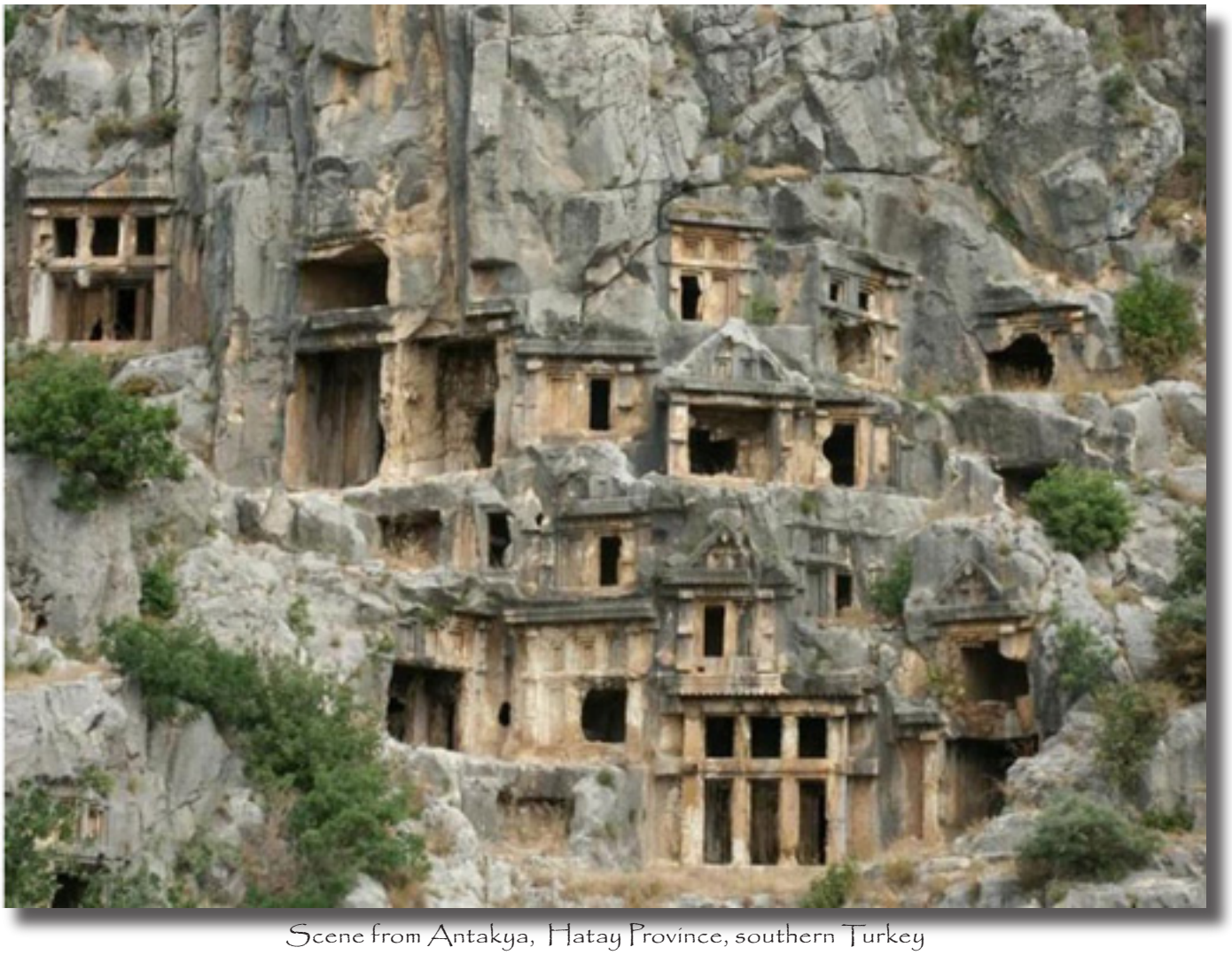

Scene from Antakya, Hatay Province, southern Turkey

# This issue: Focus on Turkey

# From the Editor

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This issue is rich with papers from Turkey and Iran that deals with important topics with interesting findings. Tarikçi Kiliç E,T et al; looked at preoperative fears caused by multiple pediatric burn surgeries. The authors stressed that burn injuries can cause anxiety, sleep affective and learning disorders among children. Hospitalized children are observed to experience nightmares, behavioral regression and post- traumatic stress disorder. This situation increases both the stress hormone levels in their blood and the morbidity and mortality rates. Pain becomes more severe while changing the wound dressings and during practices like hydrotherapy, skin grafting, physiotherapy and debridement. Therefore, a good pain and anxiety control should be achieved especially to avoid pain during treatment, to help children heal more easily, and to reduce their stress.

Kooshkiforooshani, M et al ; looked at Troponin I level changes following diagnostic coronary angiography. A total of 280 patients with normal baseline CTnI level and normal coronary angiography or mild stenosis were included. Serum CTnI level was measured by ELISA method at baseline and once more during 6 to 24 hours after coronary angiography. None of the patients experienced chest pain, dyspnea, arrhythmia, malignant hypertension, or ECG changes. The authors concluded that serum cTnI level can elevate after coronary angiography in a small percentage of patients with mild CAD. Male gender, diabetes mellitus, hypertension, obesity, and chronic kidney disease were factors associated with this elevated cTnI level.

Mehmet MR et al looked at the association of Malignancies in sickle cell diseases. All patients with the SCDs and age and sex-matched controls were studied. The study included 428 patients with the SCDs (220 males) and 518 controls (266 males). Although various malignancies were diagnosed in 11.5% of the control cases (23 females and 37 males), this ratio was only 0.4% (one female and one male) in the SCDs ($p<0.001$). The authors concluded that SCDs are chronic and severe inflammatory processes on vascular endothelium initiated at birth, and terminate with end-organ insufficiencies in early years of life. Such permanent inflammatory processes may increase clearance of malignant cells by immune system that may be the cause of significantly lower prevalence of malignancies in the SCDs.

Mehmet Rami Helvaci, MR et al looked at Varicocele and endothelial inflammation. Consecutive patients with a surgical repair history of varicocele were collected into the first and age-matched control cases were collected into the second groups. The study included 31 patients with varicocele and 80 control cases. The authors concluded that although the metabolic syndrome is a chronic low-grade inflammatory process on vascular endothelium, terminating with an accelerated atherosclerosis, end-organ failures, early aging, and premature death, varicocele may not have a chronic low-grade inflammatory background on vascular endothelium in general. On the other hand, thalassemias and other causes of splenomegaly may cause torsion of the left renal vein and prevent its drainage. So drainage problems at the level of left renal vein due to the stronger arterial walls that cannot be obstructed easily may explain the higher prevalence of varicocele and renal atrophy on the left side in the literature since the left testicular vein drains into the left renal vein.

Naseri P et al; attempted to localize self-regulation areas in response to palatable food using a Bayesian Generalized Linear Model (GLM) approach. A new proposed Bayesian approach was applied for assessing functional response to palatable food stimuli in a block design fMRI data with 370 scans of one healthy women. Regions of Interest (ROIs) including the dorsolateral and medial prefrontal cortex, the inferior frontal gyrus and the mid-ventrolateral frontal cortex were investigated. The results of the present revealed that palatable food as compared to non-food images elicit stronger activation in brain self-regulation areas including the dorsolateral and medial prefrontal cortex, the inferior frontal gyrus and the mid-ventrolateral frontal cortex. The authors concluded that self-regulation areas of people who are concerned about their weight, will be activated in confrontation with palatable foods.


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# Determınatıon of Preoperatıve Fear and Anxıety Levels caused by Multıple Pedıatrıc Burn Surgeries in Patıents and theır Parents

**Hakan Akelma** (1)
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## Abstract

Background: Burn injuries can cause anxiety, and sleep affective and learning disorders among children. Hospitalized children are observed to experience nightmares, behavioural regression and post- traumatic stress disorder.

Objectives and Methods: This situation increases both the stress hormone levels in their blood and the morbidity and mortality rates. Pain becomes more severe while changing the wound dressings and during practices like hydrotherapy, skin grafting, physiotherapy and debridement.

Therefore, good pain and anxiety control should be achieved especially to avoid pain during treatment, to help children heal more easily, and to reduce their stress

Results and Conclusion: We aimed to evaluate the effects of multiple pediatric burn surgeries on the pediatric patients and their parents.

Key words: Burn injuries, pain, anxiety, pediatric, parents.

## Introduction

Anxiety is a universal response to any perceived dangers or threats that cause distress in an individual (1). In other words, it is an unpleasant emotional state which is experienced as feelings of uneasiness, worry or foreboding that are often accompanied by certain physiological symptoms. The individual perceives it as a feeling of unrealistic worry and tension as if something bad is going to happen. This feeling can vary in intensity from slight uneasiness and tension to severe panic (2).

Spielberger defined two distinct kinds of anxiety: state and trait anxiety. State anxiety is a subjective fear that the individual feels due to a specific stressful situation. As a result of an activation of the autonomic nervous system, the tension and unease can also be manifested as physiological symptoms such as sweating, looking pale, flushing and shaking. Trait anxiety, on the other hand, is the tendency of the individual to perceive or interpret every situation as stressful because of his/her inclination to worry. People with a high level of chronic anxiety are observed to be vulnerable and pessimistic individuals(3).

There are many causes of burn injuries. It is a type of injury that can occur due to various causes such as hot liquids, electrical devices, chemical substances and gas explosions, and that can be avoided through preventive steps (4,5). Burn injuries are someof the most serious traumas and affect patients both physiologically and psychologically. They cause pain and incur a major stress

response until they heal. Burn injuries are classified as distinct from other types of injuries owing to certain factors including the severe pain during or after the injury, the changes in the body image of patients and the relatively long treatment period. In our country over 5,000 children are hospitalized and treated for burn injuries annually. 40% of the hospitalized burn injury patients are children. Children aged 1 to 5 years have the highest incidence of burn injuries.

Burn injuries can cause anxiety, sleep, affective and learning disorders among children. Hospitalized children are observed to experience nightmares, behavioural regression and post-traumatic stress disorder. This situation increases both the stress hormone levels in their blood and the morbidity and mortality rates. Pain becomes more severe while changing the wound dressings and during practices like hydrotherapy, skin grafting, physiotherapy and debridement. Therefore, a good pain and anxiety control should be achieved especially to avoid pain during treatment, to help children heal more easily, and to reduce their stress ( 6,7). Burn care requires a multidisciplinary team consisting of doctors, nurses, dieticians, incident managers, social workers and other related health care employees who treat the burned patient.

The surgical process can be stressful for parents. , It has been shown that increased anxiety levels of parents can indirectly affect the anxiety level of children and when the anxiety levels of the parents are lowered, the anxiety levels of the children and therefore their need for postoperative analgesic medication can also be reduced (8).

The factors that can affect parental anxiety are classified in literature as follows: lack of knowledge about the treatment method, unfamiliar surroundings, type of anesthesia, the fear that their child will not wake up after surgery, the fear that they will lose their child, the pain their child feels. There are also additional factors such as being isolated from social life, having to communicate with strangers, medical terminology used by the health care team, and contact with unfamiliar medical devices.
In this study we aimed to identify the effects of multiple pediatric burn surgeries on the pediatric patients and their parents.

## Materials and Methods

This study was approved by the Ethical Committee of Gazi Yaşargil Training and Research Hospital School of Health Sciences and was conducted on 200 pediatric ASA1 and ASA2 patients aged between 2-16 who had minimum 2 and maximum 6 surgeries in the Burn Center of the hospital and 200 parents who accompained them. Written consent was obtained from those parents who were able to understand the scales or fill them out with the help of someone they knew.

Surgeons applied Modified Yale Preoperative Anxiety Scale and Smiley Faces Scale to all the patients 30 minutes before the surgery (Chapman and Kirby-Turner, 2002). 30 minutes prior to the surgery the parents were given The State-Trait Anxiety Inventory (STAI) and their points were added up.

Modified Yale Preoperative Anxiety Scale and Smiley Faces Scale, which enable the doctors to observe and evaluate the behaviors of the patients before the surgery, were applied to patients 30 minutes prior to the surgery. To evaluate the anxiety levels of the parents, the literate ones were given STAI-1 (The State-Trait Anxiety Inventory) 30 minutes before the surgery. The illiterate ones were read STAI-1 (The State-Trait Anxiety Inventory) by the doctors in a quiet room 30 minutes prior to the surgery in the presence of someone they knew. All the patients were given 0.01 mg/kg midazolam and 10 mg ketamine in the preoperative room before they were separated from their parents and then taken to the operating room. To monitor the vital parameters of the patients in the operating room, peripheral pulse oximeter, ECG and non-invasive arterial blood pressure monitoring methods were used.

This study excluded patients who were operated on only once or more than six times; patients who had previous surgery in their anamnesis and their parents, parents who could not be contacted, parents who had previously received psychiatric treatment due to anxiety, and parents whowere being treated for a chronic disease.

**Statistical analysis**
The Statistical Package for the Social Sciences software version 16.0, Chicago, IL, USA was used. The data was analyzed in terms of correspondence to normal distribution. Demographic data has been presented about the duration of anesthesia, the severity and percentage of the burns, average surgery time and standard deviation; gender has been presented in numbers and percentages.

Cronbach's Alpha was used to measure reliability of the scale. The Independent Samples Test was used to compare the means of two independent groups in order to determine whether there was statistical evidence that the associated population means are different, and Mann Whitney U test was used when the assumptions could not be met. Levene's Test was used to evaluate the homogenity of the two study groups. Statistical significance level was chosen as $p \geq 0.05$ in all tests.

## Results

From the patients included in the study, 90 were male (45 %) and 110 were female (55 %). The age of the patients varied between 2 and 15, and the mean age was 4,32 ± 3. The causes of burn injuries were hot water (79,8 %), hot food (10.9), flame (4.4 %), hot milk (1.5 %) and others (3.4 %). (Figure 1 - next page)

The mean surgery duration was 28.69 minutes, the mean hospital stay was 6.36 days, the mean number of surgeries was 2.56, the mean burned total surface area was 9.75 %, the mean burn depth was 2.17, and the mean age was 4.32. (Table 1 - next page)

**Figure 1: Distribution of the Causes of Burns**

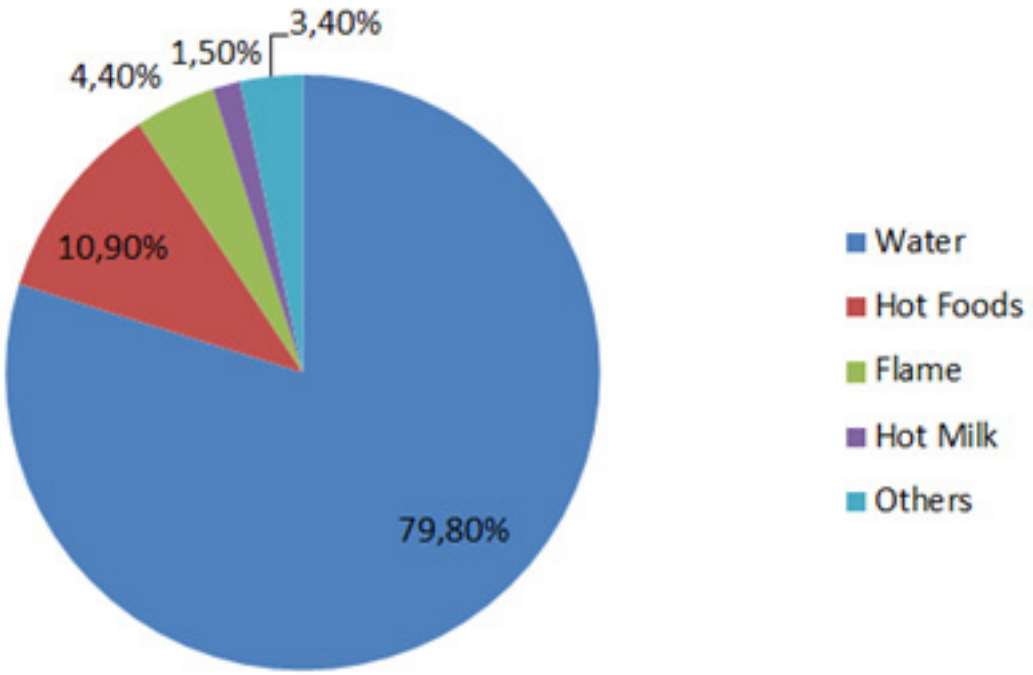



**Table 1: Descriptive Statistics**

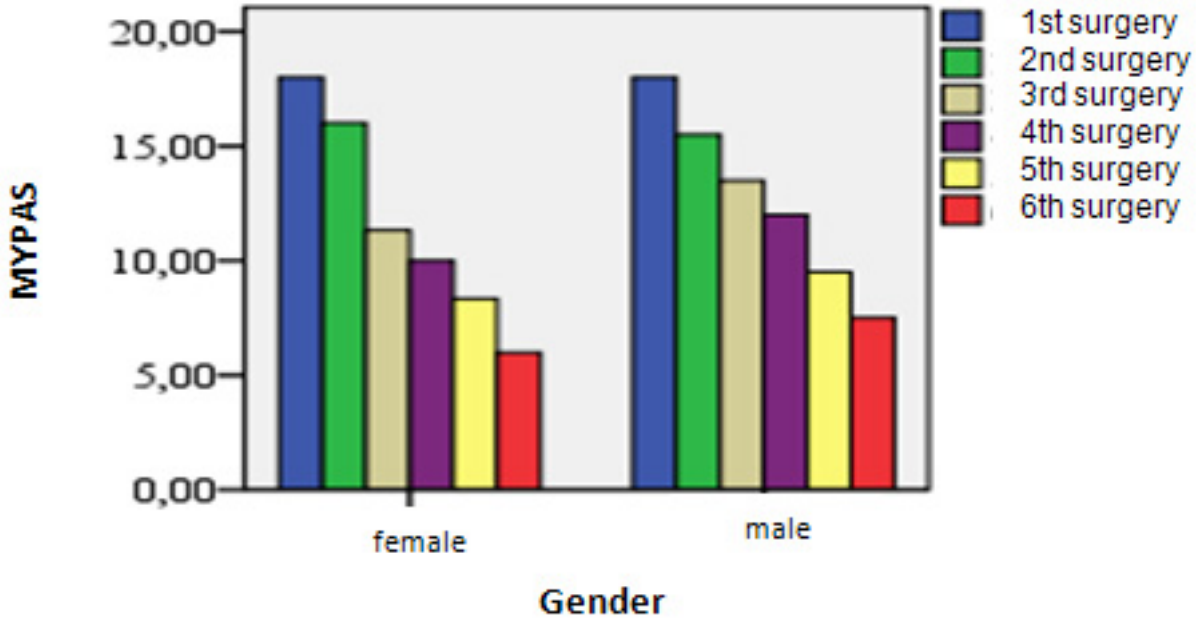
| | N | Minimum | Maximum | Mean | Standard Deviation | Variance |
|---|---|---|---|---|---|---|
| NUMBER OF SURGICAL PROCEDURES | 200 | 2.00 | 6.00 | 2.5600 | 1.08544 | 1.178 |
| DURATION OF SURGERY (MINUTES) | 200 | 15.00 | 52.00 | 2.6900 | 7.29619 | 61.052 |
| HOSPITAL STAY(DAY) | 200 | 2.00 | 50.00 | 6.3600 | 7.11169 | 52.234 |
| TOTAL BURNED SURFACE AREA (%) | 200 | 2.00 | 35.00 | 9.7500 | 6.35383 | 40.371 |
| BURN DEPTH | 200 | 2.00 | 3.00 | 2.1700 | .37753 | .143 |
| AGE (YEAR) | 200 | 2.00 | 15.00 | 4.3200 | 2.99117 | 8.947 |
| NUMBER OF CHILDREN | 200 | 1.00 | 10.00 | 3.5900 | 1.84279 | 3.396 |

The education level of the parents included in the study are as follows: 54% of the mothers were illiterate, 34% were primary school graduate, 10% were high school graduate and 2% were university graduate; 18% of the fathers were illiterate, 57% were primary school graduate, 23% were high school graduate, 2% were university graduate.

70% of the families owned the house they lived in, while 30% of the families were renters. 74% of the families had nuclear households and 36% had extended households. 34% of the families migrated to the city they lived in, while 66% of them were born there.

It can be seen that the mean scores in the Modified Yale Preoperative Anxiety Scale decreased in both female and male patients as they went through multiple surgeries (Figure 2

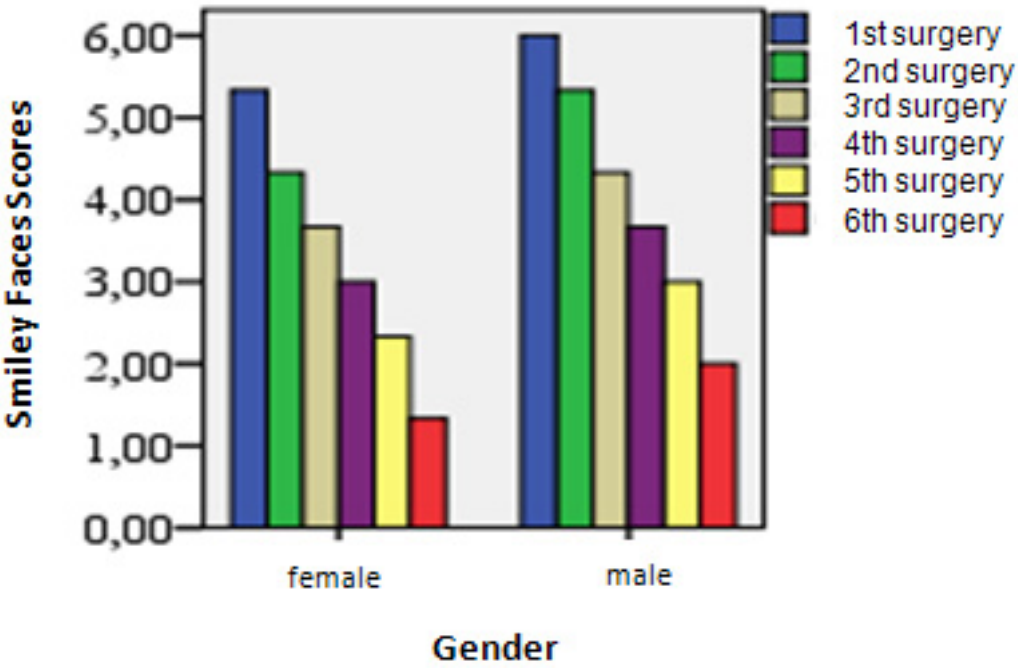
**Figure 2: Comparison of the Modified Yale Preoperative anxiety levels in female and male patients**




Mann Whitney U Test was used to compare the differences in the anxiety levels of female and male patients. The results of the comparison between the anxiety levels of females and males showed $p>0.05$ in all preoperative scores and no significant statistical difference was found between the two groups.

When the Smiley Faces Scale scores were compared, it can be seen that the anxiety levels of both female and male patients decreased with multiple surgeries (Figure 3).

**Figure 3: Comparison of Smiley Faces Scale scores of female and male patients**




Mann Whitney U Test was used to compare the differences in the anxiety levels of female and male patients. The results of the comparison between the anxiety levels of females and males showed $p>0.05$ in all preoperative scores and no significant statistical difference was found between the two groups.

There is a statistical correlation between Modified Yale Preoperative Anxiety Scale and Smiley Faces Scale ($p<0.05$) (Chapman and Kirby-Turner, 2002).

**Table 2: The Correlation between Smiley Faces Scale and Modified Yale Preoperative Anxiety Scale**

| Number of Surgical procedures | N | Minimum | Maximum | Mean | Standard Deviation | Variance |
|---|---|---|---|---|---|---|
| m-YPAS 1 | 200 | 5,00 | 22,00 | 14,0500 | 3,48264 | 12,129 |
| m-YPAS 2 | 200 | 5,00 | 20,00 | 10,1400 | 3,51338 | 12,344 |
| m-YPAS 3 | 58 | 5,00 | 20,00 | 10,4138 | 3,36492 | 11,323 |
| m-YPAS 4 | 26 | 5,00 | 14,00 | 9,0769 | 2,84199 | 8,077 |
| m-YPAS 5 | 12 | 6,00 | 10,00 | 8,5000 | 1,64317 | 2,700 |
| m-YPAS 6 | 10 | 5,00 | 8,00 | 6,6000 | 1,14018 | 1,300 |
| SMILEY FACES 1 | 200 | 2,00 | 6,00 | 4,9900 | ,95869 | ,919 |
| SMILEY FACES 2 | 200 | 1,00 | 6,00 | 3,2700 | 1,20483 | 1,452 |
| SMILEY FACES 3 | 58 | 2,00 | 5,00 | 3,2414 | ,91242 | ,833 |
| SMILEY FACES 4 | 26 | 2,00 | 4,00 | 2,7692 | ,83205 | ,692 |
| SMILEY FACES 5 | 12 | 2,00 | 4,00 | 2,6667 | ,81650 | ,667 |
| SMILEY FACES 6 | 12 | 1,00 | 3,00 | 1,6667 | ,81650 | ,667 |

In this study, Modified Yale Preoperative Anxiety Scale and Smiley Faces Scale were used to determine the preoperative anxiety levels of the patients. It was found that the mean anxiety scores of patients measured prior to each surgery declined as they underwent multiple surgical procedures (Cronbach's Alpha=0.954) (Table 2).

When the results of STAI-1 questionnaires that were filled out 30 minutes prior to the surgery were analyzed with the Student's T Test, they showed homogeneity of variance according to the Levene Test ( $p>0.05$ ). No significant statistical difference was found between parents' level of education and their anxiety levels ( $p>0.05$).

It was found that 23% of the groups worked for minimum wage or above the minimum wage, while 77% earned less than the minimum wage. The parents in the study were homogenously grouped in terms of their income level (Levene Test $p>0.05$) and Independent Samples T Test showed no significant statistical difference between the anxiety level of the groups ($p>0.05$). As the number of patients who underwent more than 4 surgeries was not adequate to form an effective sample, those patients were excluded from the study.

34% of the families migrated to the city they lived in, while 66% of them were born there. The families were given Mann-Whitney U Test after the scores of STAI-1 the State-Trait Anxiety Inventory were collected. No significant statistical difference was found between the migrant and native groups ($p>0.05$).

When the Mann-Whitney U Test was applied to the mean scores from STAI-1 The State-Trait Anxiety Inventory of the families who owned a house and those who were tenants, no significant statistical difference was found between the two groups ($p>0.05$).

When the mean scores from STAI-1 inventory of nuclear and extended families were compared with the Mann-Whitney Test, a significant statistical difference was found ($p<0.05$) (Table 3).

**Table 3: STAI Anxiety Inventory Scores of Family Types**

| TYPE OF FAMILY STRUCTURE | N | STAI mean rank | Number of Surgeries |
|---|---|---|---|
| NUCLEAR | 148 | 47,57 | 1 |
| EXTENDED | 52 | 58,83 | 1 |
| Total | 200 | | |
| NUCLEAR | 148 | 46,15 | 2 |
| EXTENDED | 52 | 62,88 | 2 |
| Total | 200 | | |
| NUCLEAR | 32 | 13,12 | 3 |
| EXTENDED | 20 | 14,10 | 3 |
| Total | 52 | | |
| NUCLEAR | 16 | 5,19 | 4 |
| EXTENDED | 10 | 9,90 | 4 |
| Total | 26 | | |
| NUCLEAR | 6 | 2,00 | 5 |
| EXTENDED | 6 | 5,00 | 5 |
| Total | 12 | | |
| NUCLEAR | 6 | 2,00 | 6 |
| EXTENDED | 6 | 5,00 | 6 |
| Total | 12 | | |

When the anxiety levels of families with 3 and more children and those with fewer than 3 children were compared by Student T test, no significant statistical difference was found between the two groups ($p>0.05$).

When the scores of the parents of children with second and third-degree burns were compared by Student T test, no significant statistical difference was found in patients and their parents ($p>0.05$).

In this study, STAI-1 State-Trait Anxiety Inventory was used to measure the anxiety levels of the parents 30 minutes prior to surgery. Anxiety mean scores which were measured before each surgery were observed to decrease with each surgery (Cronbach's Alpha=0.838).

## Discussion

The main purpose of this study was to determine the anxiety levels of children who underwent surgery due to burn injuries, and of their parents, and to find out the changes in the anxiety levels through multiple surgical procedures. The results of this study show that the anxiety levels of the burn injury patients and their parents decrease with each surgery the patient undergoes. Caumo and his colleagues found out that 346 of the 592 patients who underwent elective surgery had previous surgical operations and that the anxiety levels were lower in this group. They explained the lower anxiety levels in patients who had undergone surgery before with conditional learning model (9). Erdem and his colleagues also obtained similar results and reported that previous surgical experience decreases preoperative anxiety. The study conducted by Duman and his colleagues supported the conditional learning model and reported that the patients who had undergone surgery previously had lower anxiety levels (10, 11). According to the definition of conditional learning model, an unconditional fear stimulus must be encountered at short intervals. In this study, we measured the m-YPAS mean scores of the patients who had surgery for the first time as 14±3.5 and their Smiley Faces Scale mean scores as 5±0.9. M-YPAS mean scores were measured 10±3.5 in the second surgery, 10±3.3 in the third surgery, 9 in the fourth surgery, 8.5 in the fifth surgery, and 6.6 in the sixth surgery. Smiley Faces Scale mean scores of the patients were measured 3.27 in the second surgery, 3.24 in the third surgery, 2.76 in the fourth surgery, 2.66 in the fifth surgery, and 1.66 in the sixth surgery. Smiley Faces and m-YPAS scales were correlated and as the number of surgical procedures goes up, the mean scores go down. We also think that this situation is related to the fact that the patients learn through encountering the fear stimulus at short intervals.

Li and Lam measured the mean preoperative state anxiety level as 43.7 in their study on 112 pediatric patients and their parents. It was reported in the study conducted by Karaca Çiftçi and her colleagues that the parents with children who were to undergo a surgical intervention experienced a moderate-level anxiety (the state anxiety mean score was determined as 44.07). The findings of these studies are similar to our anxiety mean score prior to the first surgery (The state anxiety mean score 48.9±7.29) (12,13).

In our literature review we could not find any studies which explained the reasons behind the change in the anxiety levels of parents with children who underwent multiple surgeries. Studies in this area generally focus on the anxiety levels prior to a single surgery. This study is the first to investigate this subject. This study concludes that the anxiety levels of parents decrease as their children undergo multiple procedures.We think that this decrease is related to the decrease in their children's pain, healing of their wounds, their getting used to the hospital environment, the interval between the surgeries, and the conditional learning model.

In the case study Aygıt and his colleagues carried out, the most common cause of burn injuries among 145 patients under the age of 12 that were admitted to the burn center was scalding (86%). They reported the shortest hospital stay among the cases as 1 day, the longest stay as 48 days and the mean length of stay as 14.5±8.07; the mean number of surgery as 3.97±3.03, the mean percentage of burns as 6.68% (14). In this study, the most common cause of burn injuries was scalding (79.8%). The shortest hospital stay of the cases was 2 days, the longest hospital stay was 50 days, the mean length of hospital stay was 6.36±7.1 days, the mean number of surgeries was 2.5±1, the mean percentage of burns was 9.7±6.3, all of which are similar to the findings of Aygıt and his colleagues. In the same study, Aygıt and his colleagues pointto the fact that extended family model may have a negative impact on the pediatric burn injuries and may increase the preoperative anxiety (14). Similar to the findings of Aygıt and his colleagues, we also found that the anxiety level was significantly higher in the extended family structure ($p>0.05$).

When we look into the burn degrees of the patients admitted to the burn center, Demirel and his colleagues assessed 227 patients staying in the burn center and saw that 60.8% of them had second-degree burns and 39.2% had third-degree burns (15). In this study, 83% of the patients had second-degree burns and 17% had third-degree burns. According to the data we obtained in our study, we saw that second-degree burns were more common. We think that is because first-degree burns are ignored in our society or the patients are treated at home after the initial treatment is provided in the emergency room.

Şayık and his colleagues reported that out of the 1,121 pediatric patients aged between 0 and 18 who went to the emergency room, 56.4% were male and 43.6% were female. The size of the burned body surface area was commonly 10-19% (16). In our study, 45% of the patients were male and 55% were female. In our patients the highest percentage of burned body surface area was below 10. Although we had a different statistic from Şayık and his colleagues, we could not find a meaningful correlation between gender and burned body surface area, contrary to their findings. We think that the reason for the lower percentage of burned body surface area in our study is the fact that our intensive care unit does not hospitalize patients with large burn areas because of the physical conditions of the unit.

While Demir and his colleagues who analyzed the connection between level of education and preoperative anxiety on a group of 100 patients pointed out that anxiety level increased with an increasing level of education, in the study conducted by Turhan and his colleagues which included 120 patients it was found that educational level of the patients did not affect preoperative anxiety levels. In our study, we compared the anxiety levels of the parents who received education for at least five years with those who studied over a five year period, we identified that there was no connection between the anxiety levels of parents and their level of education (17, 18).

Unlike Demir and his colleagues, we could not see a statistically significant relation between socioeconomic status and preoperative anxiety. There can be great differences in the socioeconomic status of people in the society. Besides, burn injuries can occur in both low and high income households (18). When our findings were evaluated, we can say that anxiety levels are not related to income.

Karaca Çiftçi and her colleagues compared parents with 3 or more children (67.5%) with those with fewer than 3 children (%32.5) in terms of preoperative anxiety levels and found that those with a higher number of children had a higher level of anxiety. They stated the reason for that as the decrease in the time allocated to other children (12). In our study 65% of parents had fewer than 3 children and there was no significant statistical difference between the two groups.

We think that the anxiety levels of the patients and their parents are not affected by demographic variables and severity of burns because the initial treatment is provided timely, the patients receive the right dosage of analgesic medications, and both the patients and their parents adjust to the burn center. We also think that the lack of difference between the anxiety levels of the patients can be because our burn center staff accompany the patients to their rooms, show them around the room and give them orientation to the center; the patients can reach the nurses whenever they need and they are given information about everything; the primary doctor and the anaesthetist visit the patients in their rooms prior to and after the surgery.

When different scales and studies are considered, it is hard to make meaningful comparisons among the findings of anxiety studies due to the differences in scales, methods and procedures. Scales differ in terms of the measurement of response type, the process conducted, and their implementation. In our study, STAI-1 state-trait anxiety inventory was used to measure the anxiety levels of the parents and Modified Yale Preoperative Anxiety Scale and Smiley Faces Scale were used on pediatric patients. The scores of the anxiety scales used on pediatric patients may vary as they were based on the observations of the doctors. When these possible differences in scores and the fact that there is little research available on the anxiety caused by multiple surgical procedures are taken into consideration, we think that more studies are required to verify our findings.

There were two major limitations of the study. Firstly, as it was carried out only in the burn center of our research hospital, the results of the study cannot be generalised to other burn patients. Secondly, the study was really time-consuming as it involved patients with burn injuries.

## Conclusion

In this study which focused on the measurement and evaluation of the anxiety levels of preoperative patients and their parents and on whether there were statistically significant differences based on the distinct qualities of patients and their parents, we found out that there were no statistically significant differences in the anxiety levels of the groups when they were compared in terms of education level, home ownership, migration status and income. When the family structures were compared, the results demonstrated a statistically significant difference in anxiety levels of members of extended families and nuclear families, and it was revealed that the anxiety levels in the extended family structure were higher ($p<0.05$). In the study, the mean score of the STAI-1 anxiety scale was measured as 48.9±7.29 for the parents, and the mean score of the m-YPAS scale was measured as 14±3.5 and that of Smiley Faces Scale measured as 4.9±0 for the pediatric patients prior to the first surgery, and we concluded that the anxiety levels decreased with multiple surgeries.

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# Troponin I level changes following diagnostic coronary angiography

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## Abstract

Background: There is evidence that cardiac biomarkers may rise after coronary angiography. We decided to determine elevated cardiac troponin I (cTnI) after coronary angiography in patients with normal coronary artery or < 50% stenosis. In addition, association of cTnI elevation with conventional CAD (coronary artery disease) risk factors was investigated.

Materials and Methods: A total of 280 patients with normal baseline CTnI level and normal coronary angiography or mild stenosis (defined as less than 50% stenosis) were included. Serum CTnI level was measured by ELISA method at baseline and once more during 6 to 24 hours after coronary angiography. Normal serum cTnI was < 1.3 ng/mL. In all patients, 6 French catheters were used and the contrast media was Ultravist with osmolality of 328 mOsm/kg.

Results: Elevated post-procedural CTnI was documented in seven patients (2.5%) with a mean value of 1.9 ng/mL (1.45 to 2.2 ng/mL). None of the patients experienced chest pain, dyspnea, arrhythmia, malignant hypertension, or ECG changes. There were more patients with male gender (4.9% vs. 0.6%), diabetes mellitus (6.3% vs. 0.5%), chronic kidney disease (20% vs. 1.1%), and obesity (8.9% vs. 1.6%) in the elevated cTnI level group than those who did not experience troponin rise (P< 0.01). All elevated cTnI group patients were hypertensive.

Conclusion: Serum cTnI level can elevate after coronary angiography in a small percentage of patients with mild CAD. Male gender, diabetes mellitus, hypertension, obesity, and chronic kidney disease were factors associated with this elevated cTnI level.

Key words: Troponin; coronary; angiography

## Introduction

Cardiac troponin I (cTnI) is a specific marker for myocardial injury. It has better sensitivity and specificity over creatine kinase (CK) for myocardial injury (1). Troponins are structural proteins that are released into the bloodstream as a result of myocyte membrane disruption caused by myocardial injury (2). Hence, these markers are used for both diagnostic and prognostic purposes in acute coronary syndrome (ACS) (3).

Under normal condition, cardiac troponins are not present in the bloodstream. In addition to myocyte injury, cardiac troponins may increase in some other conditions such as skeletal muscle damage and heart failure (2). Another important condition where cardiac troponins can rise is following interventional cardiac procedures. There is evidence that peri-procedural troponin rises (1, 4-7). This post-procedural rise is important as it can reflect two conditions, namely myocardial infarction or myocardial necrosis due to the procedure itself (2). Most studies have emphasized on troponin rise after percutaneous coronary interventions (PCI) with an incidence of 10 to 40% (8). In a meta-analysis of more than 7,000 patients, MI was found in 15% of patients after PCI and this was associated with a higher rate of adverse events at 18 months follow-up (9). This was confirmed in another meta-analysis on 22,000 patients where increased cTnI was documented in 34% of patients whose all-cause mortality was significantly higher compared to other patients who did not have cardiac troponin rise (1).

Limited studies have been performed regarding cardiac troponin rise after coronary angiography. In a study on 12 patients younger than 21 years who underwent cardiac catheterization (mostly angiography), elevated cTnI was observed in 79% of patients immediately after catheterization and just two patients had myocardial injury (10).

As there is limited data about cardiac troponin rise after coronary angiography and the fact that this procedure is one of the most widely used procedures in diagnosis of coronary artery disease (CAD), we intended to determine the prevalence of cTnI rise after coronary angiography and related electrocardiographic and clinical variables.

## Materials and Methods

In this cross-sectional study conducted from 2013 to 2015 at our university hospital cardiology department, 280 patients who underwent coronary angiography (left and right) and were found to have mild CAD were included consecutively. Inclusion criteria were normal CTnI level at baseline, normal coronary angiography or mild stenosis (defined as less than 50% stenosis in coronary arteries which did not cause hemodynamic disturbances at regular activities). Those with elevated baseline CTnI or other cardiac markers, or occurrence of adverse events (coronary artery dissection or rupture, emboli) during angiography, left ventricular ejection fraction (LVEF) < 40%, myocardial infarction (MI) during the last 2 weeks, stent placement requirement during angiography, cerebrovascular accident after angiography, and coronary spasm of more than 1 minute, were excluded.

Before angiography, serum cTnI level was measured by ELISA method (Monobind kit). Once more in 6 to 24 hours after angiography, serum cTnI level was assayed. In patients who showed elevated post-procedural troponin rise, its level was assayed for the second time in less than 24 hours. Normal serum cTnI was ≤ 1.3 ng/mL.

The gathered variables included age, gender, body mass index (BMI), systolic and diastolic blood pressure, serum lipid profile (total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglyceride), chronic kidney disease, conventional CAD risk factors (hypertension, hyperlipidemia, diabetes mellitus (DM), and smoking), serum creatinine, and angiography-related variables (the volume of contrast media, duration (time interval from catheter introduction to femoral artery to its removal), and number of views).

### Statistics

The descriptive indices including frequency, percentage, median (range), mean and its standard deviation (SD) were used to express data. In order to compare nominal variables between the two groups, the Chi-square test or the Fisher's exact test was used. Significance level was set at 0.05. All analyses were performed using SPSS software (ver. 16.0, IBM).

### Ethics

The study protocol was fully supported by the Research Council Ethics Committee of our medical university. The study objectives were explained to the patients and they were asked to provide written consent for enrolment. The study was in conformity with the Declaration of Helsinki.

## Results

There were 120 (43%) male and 160 females (57%) with a median age of 58 years (range, 38 to 65 years). Mean (range) systolic and diastolic BP values were 135 (115 to 155) and 85 (60 to 95) mmHg. Mean (range) BMI value was 28.5 (23.5 to 34) kg/m$^2$. Thirty-three patients were obese (BMI > 30 mg/m$^2$). Table 1 presents frequency distribution of conventional coronary artery disease (CAD) risk factors. Twenty patients had CKD. Median (range) of total cholesterol, HDL, LDL, and triglyceride levels were respectively 230 (175-280), 38 (30-48), 135 (90-195), and 210 (185-310) mg/dL.

**Table 1: Frequency of conventional coronary artery disease (CAD) among 280 patients who underwent coronary angiography**

| Variable | N (%) |
|---|---|
| Hypertension | 126 (45%) |
| Hyperlipidemia | 64 (22.8%) |
| Cigarette smoking | 59 (21%) |
| Diabetes mellitus | 95 (34%) |
| Family history of CAD | 22 (7.8%) |

In all patients, 6 French catheters were used and the contrast media was Ultravist with osmolality of 328 mOsm/kg. Coronary spasm occurred in 20 patients (7.1%). Table 2 presents coronary angiography-related variables.

**Table 2: Coronary angiography-related variables among 280 patients who underwent coronary angiography**

| Variable | Median (range) |
|---|---|
| Angiography duration, minutes | 8 (6 to 15) |
| Contrast agent volume, mL | 35 (15 to 55) |
| Number of catheters | 2.2 (2 to 4) |
| Number of views | 5 (4 to 9) |

Elevated post-procedural CTnI was documented in seven patients (2.5%) with a mean value of 1.9 ng/mL (1.45 to 2.2 ng/mL). None of the patients experienced chest pain, dyspnea, arrhythmia, malignant hypertension, or ECG changes. Characteristics of seven patients who experienced elevated cTnI

There were more males in this group (6 males, 86%) in comparison to those who did not have elevated cTnI levels. About 4.9% of males experienced cTnI elevation which was significantly higher than females (0.6%) (P< 0.01). Of seven patients who experienced elevated cTnI, four subjects (57%) had CKD and three cases were under hemodialysis. In other words, 20% of patients with CKD experienced elevated post-procedural cTnI elevation, but, only 1.1% of patients with normal renal function experienced elevated cTnI elevation (P< 0.01). Also, of seven patients, six had DM (86%). The percentage of diabetics who had elevated cTnI level after angiography (6.3%) was significantly higher than in non-diabetics which was 0.5% (P< 0.01). About 8.9% of obese patients had elevated cTnI and this figure was significantly higher than in non-obese patients (1.6%); P< 0.01. Mean duration of DM in those who had elevated cTnI was six years which was similar to non-diabetic subjects. All seven patients had hypertension. None of them were smokers. Mean LDL, contrast media volume, angiography duration, number of catheters, and number of views were respectively 150 mg/dL, 30 mL, 9 minutes, 2.5, and 5 in this group and was comparable to those who did not have cTnI elevation. None of the patients in this group had coronary spasm.

## Discussion

Coronary angiography is one of the most widely used diagnostic methods for diagnosis of CAD and risk stratification and treatment planning. Cardiac troponin rise after percutaneous cardiac catheterization can occur due to several factors and this rise can be worrisome as this may reflect myonecrosis. According to the presented findings, a small number of patients (2.5%) experienced post-coronary angiography cTnI level elevation. The reported incidence of elevated cardiac biomarkers after PCI has a wide range from 1% to 30% (9). Cardiac troponins are the most widely used in different studies owing to the sensitivity and specificity of troponins for myocyte injury. The term PCI-related MI is an established diagnosis and is described as a three-time elevation of troponin of the upper reference limit (11). None of the current patients fulfilled this definition for MI.

Troponin level rise after PCI (25 to 34%) (1) is much higher than what we observed here. Unfortunately we were not able to follow the patients to find any association between elevated cTnI level and prognosis. However, Post-PCI troponin level increase has been demonstrated to associate with all-cause mortality (1). However, there is conflicting data about to what extent measuring troponin changes and its elevation can predict long-term prognosis (5).

We found that patients who experienced elevated cTnI after coronary angiography were more likely to be male, hypertensive, diabetic, and have CKD. However, it should be considered that troponin rise after cardiac catheterization is a multifactorial phenomenon. Here, we included patients who were candidates for non-emergent diagnostic angiography and excluded heart failure patients. In previous studies, heart failure, CAD, and the requirement for urgent interventions were described as factors that are most likely to be associated with post-procedure troponin rise (12). Another important contributor to this finding is development of adverse events (vessel rupture and thrombus formation) that can cause troponin elevation (1, 6).

Whether routine measurement of troponin levels when diagnostic angiography of the coronary arteries should be made or not is still questionable. Even routine troponin measurement after PCI is not agreed on all experts (13). In contrast, there is evidence that even microleak of troponins should not be ignored and routine measurement of troponins should be made in all patients (7).

We recommend that further studies include more patients and to follow them for a longer time to find any association between elevated cTnI level after angiography and development of CAD and mortality. In addition, more interventional studies can be performed regarding some interventions that have been suggested about protective role for myonecrosis such as statins, for better understanding of this association (1).

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## Conclusion

Serum cTnI level can elevate after coronary angiography in a small percentage of patients with mild CAD. Male gender, diabetes mellitus, hypertension, obesity, and chronic kidney disease were factors associated with this elevated cTnI level.

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# What a low prevalence of malignancies in sickle cell diseases

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## Abstract

Background: We tried to understand whether or not there is a lower prevalence of malignancies due to chronic vascular endothelial inflammation in the sickle cell diseases (SCDs).

Methods: All patients with the SCDs and age and sex-matched controls were studied.

Results: The study included 428 patients with the SCDs (220 males) and 518 controls (266 males). Mean ages of the SCDs patients were similar in males and females (30.6 versus 30.1 years, respectively, p>0.05). Both smoking (24.0% versus 6.2%) and alcohol (5.0% versus 0.4%) were higher in males with the SCDs (p<0.001 for both). Although various malignancies were diagnosed in 11.5% of the control cases (23 females and 37 males), this ratio was only 0.4% (one female and one male) in the SCDs (p<0.001). On the other hand, transfused units of red blood cells in their lives (47.6 versus 28.4, p=0.000), chronic obstructive pulmonary disease (25.4% versus 7.2%, p<0.001), ileus (7.2% versus 1.4%, p<0.001), cirrhosis (7.2% versus 1.9%, p<0.001), leg ulcers (20.0% versus 7.2%, p<0.001), digital clubbing (14.0% versus 6.2%, p<0.001), coronary artery disease (18.1% versus 12.9%, p<0.05), chronic renal disease (10.4% versus 6.2%, p<0.05), and stroke (12.2% versus 7.6%, p<0.05) were all higher in males with the SCDs.

Conclusion: SCDs are chronic and severe inflammatory processes on vascular endothelium initiated at birth, and terminate with end-organ insufficiencies in early years of life. Such permanent inflammatory processes may increase clearance of malignant cells by the immune system and that may be the cause of significantly lower prevalence of malignancies in the SCDs.

Key words: Chronic vascular endothelial inflammation, sickle cell diseases, malignancies, immunologic activation

## Introduction

Chronic endothelial damage may be the major cause of aging and associated morbidity and mortalities by causing disseminated tissue hypoxia all over the body. Much higher blood pressure (BP) of the afferent vasculature may be the major underlying cause, and probably whole afferent vasculature including capillaries are involved in the process. Some of the well-known accelerators of the inflammatory process are physical inactivity, excess weight, smoking, and alcohol for the development of irreversible consequences including obesity, hypertension (HT), diabetes mellitus (DM), cirrhosis, peripheric artery disease (PAD), chronic obstructive pulmonary disease (COPD), chronic renal disease (CRD), coronary artery disease (CAD), mesenteric ischemia, osteoporosis, and stroke, all of which terminate with early aging and premature death. They were researched under the title of metabolic syndrome in the literature, extensively (1, 2). Similarly, sickle cell diseases (SCDs) are severe and permanent inflammatory processes on vascular endothelium initiated at birth, and terminate with end-organ insufficiencies in early years of life. Hemoglobin S causes loss of elastic and biconcave disc shaped structures of red blood cells (RBCs). Probably loss of elasticity instead of shape is the major problem since sickling is rare in peripheric blood samples of the SCDs with associated thalassemia minors, and human survival is not so affected in hereditary spherocytosis or elliptocytosis. Loss of elasticity is present during whole lifespan, but exaggerated with increased metabolic rate of the body. The hard RBCs induced severe and permanent vascular endothelial inflammation, edema, and fibrosis terminate with tissue hypoxia all over the body (3, 4). Capillary systems may mainly be involved in the process due to their distribution function for the hard bodies. We tried to understand whether or not there is a significantly lower prevalence of malignancies due to the permanent vascular endothelial inflammation in the SCDs.

## Material and Methods

The study was performed in the Medical Faculty of the Mustafa Kemal University between March 2007 and April 2016. All patients with the SCDs and age and sex-matched controls were studied. The SCDs were diagnosed with the hemoglobin electrophoresis performed via high performance liquid chromatography (HPLC). Medical histories of SCDs patients including smoking habit, regular alcohol consumption, painful crises per year, transfused units of RBCs in their lives, surgical operations, leg ulcers and stroke, were learnt. Due to their cumulative atherosclerotic effects together with the SCDs, patients with a history of one pack-year were accepted as smokers, and one drink-year were accepted as drinkers. A complete physical examination was performed by the same Internist. The SCDs with acute painful crisis were treated at first, and the laboratory tests and clinical measurements were performed on the silent phase. A check up procedure including erythrocyte sedimentation rate, C-reactive protein, serum total protein and albumin, serum iron, iron binding capacity, ferritin, creatinine, hepatic function tests, markers of hepatitis A virus, hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV), a posterior-anterior chest x-ray film, an electrocardiogram, a Doppler echocardiogram both to evaluate cardiac walls and valves and to measure systolic BP of pulmonary artery, an abdominal ultrasonography, a venous Doppler ultrasonography of the lower limbs, a computed tomography of brain, and a magnetic resonance imaging (MRI) of hips were performed. Other bones for avascular necrosis were scanned according to the patients' complaints. Additional diagnostic methods including thoracic and abdominopelvic computed tomographies (CT), endoscopy, bronchoscopy, colonoscopy, tissue sample biopsies including bone marrow biopsies, and flow cytometric studies were performed according to the requirements in suspected cases of malignancies, and malignancies were diagnosed, histopathologically. Associated thalassemia minors were detected with serum iron, iron binding capacity, ferritin, and hemoglobin electrophoresis performed via HPLC. The criterion for diagnosis of COPD is post-bronchodilator forced expiratory volume in one second/forced vital capacity of less than 70% (5). An x-ray film of abdomen in upright position was taken just in patients with abdominal distention or discomfort, vomiting, obstipation, or lack of bowel movement, and ileus was diagnosed with gaseous distention of isolated segments of bowel, vomiting, obstipation, cramps, and with the absence of peristaltic activity on the abdomen. Systolic BP of the pulmonary artery of 40 mmHg or higher is accepted as pulmonary hypertension (6). CRD is diagnosed with a persistent serum creatinine level of 1.3 mg/dL in males and 1.2 mg/dL in females. Cirrhosis is diagnosed with physical examination, liver function tests, ultrasonographic evaluation, and tissue samples in case of requirement. Digital clubbing is diagnosed with the ratio of distal phalangeal diameter to interphalangeal diameter which is greater than 1.0, and with the presence of Schamroth's sign (7, 8). An exercise electrocardiogram is performed just in cases with an abnormal electrocardiogram and/or angina pectoris. Coronary angiography is taken just for the exercise electrocardiogram positive cases. So CAD was diagnosed either angiographically or with the Doppler echocardiographic findings as the movement disorders in the cardiac walls. Rheumatic heart disease is diagnosed with the echocardiographic findings, too. Avascular necrosis of bones is diagnosed by means of MRI (9). Stroke is diagnosed by the CT of brain. Sickle cell retinopathy is diagnosed with ophthalmologic examination in patients with visual complaints. Eventually, prevalence of various malignancies were detected both in the SCDs and control groups, and compared in between. Mann-Whitney U test, Independent-Samples t test, and comparison of proportions were used as the methods of statistical analyses.

## Results

The study included 428 patients with the SCDs (220 males) and 518 controls (266 males), totally. Mean ages of the SCDs patients were similar in males and females (30.6 versus 30.1 years, respectively, p>0.05). Mean ages of the control cases were 30.8 versus 30.5 years, respectively (p>0.05 for both). Prevalence of associated thalassemia minors were similar in males and females with the SCDs (72.2% versus 67.7%, respectively, p>0.05). Both smoking (24.0% versus 6.2%) and alcohol consumption (5.0% versus 0.4%) were significantly higher in males with the SCDs (p<0.001 for both) (Table 1).

**Table 1: Characteristic features of the sickle cell patients**

| Variables | Male patients with SCDs* | *p*-value | Female patients with SCDs |
|---|---|---|---|
| Prevalence | 51.4% (220) | Ns† | 48.5% (208) |
| Mean age (year) | 30.6 ± 10.1 (5-58) | Ns | 30.1 ± 9.9 (8-59) |
| Thalassemia minors | 72.2% (159) | Ns | 67.7% (141) |
| ***Smoking*** | ***24.0% (53)*** | ***<0.001*** | ***6.2% (13)*** |
| ***Alcoholism*** | ***5.0% (11)*** | ***<0.001*** | ***0.4% (1)*** |

*Sickle cell diseases †Nonsignificant (p>0.05)

Although various malignancies were diagnosed in 11.5% of the control cases (23 females and 37 males), this ratio was only 0.4% (one female and one male) in the SCDs group (p<0.001) (Table 2).

**Table 2: Comparison of the patients and control groups**

| Variables | Patients with SCDs* | *p*-value | Control cases |
|---|---|---|---|
| Number | 428 | Ns† | 518 |
| Female ratio | 48.5% (208) | Ns | 48.6% (252) |
| Mean age of males | 30.6 ± 10.1 (5-58) | Ns | 30.8 ± 10.2 (9-59) |
| Mean age of females | 30.1 ± 9.9 (8-59) | Ns | 30.5 ± 9.8 (10-58) |
| ***Prevalence of malignancies*** | ***0.4% (2)*** | ***<0.001*** | ***11.5% (60)*** |

*Sickle cell diseases †Nonsignificant (p>0.05)

There were nine patients with Hodgkin's lymphoma, six with acute lymphoblastic leukemia, five with acute myelogenous leukemia, five with Ph-positive chronic myelocytic leukemia, four with CD20-positive diffuse large B-cell lymphoma, four with sarcoma (Ewing's sarcoma, liposarcoma, soft tissue sarcoma, and osteosarcoma), three with ovarian cancer, three with breast cancer, three with colorectal cancer, three with lung cancer (two non-small cell and one small cell carcinomas), two with follicular lymphoma, two with chronic lymphocytic leukemia, two with multiple myeloma, two with T-cell lymphoma, one with medulloblastoma, one with stomach cancer, one with hepatocellular carcinoma (HCC) in the presence of hepatitis B surface antigen (HBsAg) positivity, one with Burkitt's lymphoma, one with primary peritoneal carcinomatosis, one with testicular cancer, and one with malignant epithelial tumor in the control group. Whereas there was just a breast cancer in a female and a non-small cell carcinoma of lung in a male with the SCDs (p<0.001 both for females and males). On the other hand, transfused RBC units in their lives (47.6 versus 28.4 units, p=0.000), COPD (25.4% versus 7.2%, p<0.001), ileus (7.2% versus 1.4%, p<0.001), cirrhosis (7.2% versus 1.9%, p<0.001), leg ulcers (20.0% versus 7.2%, p<0.001), digital clubbing (14.0% versus 6.2%, p<0.001), CAD (18.1% versus 12.9%, p<0.05), CRD (10.4% versus 6.2%, p<0.05), and stroke (12.2% versus 7.6%, p<0.05) were all higher in males with the SCDs, significantly. There were two cases with sickle cell retinopathy in males and one in females (p>0.05). There were 30 mortality cases (16 males) during the ten-year follow-up period. The mean ages of mortality were 30.8 ± 8.3 years (range 19-50) in males and 33.3 ± 9.2 years (range 19-47) in females (p>0.05) (Table 3 - next page). Beside these, there were four patients with HBsAg positivity (0.9%) but HBV DNA was positive in none of them by polymerase chain reaction (PCR) method. Although antiHCV was positive in 5.8% (25) of the study cases, HCV RNA was detected as positive just in three (0.7%) by PCR.

**Table 3: Associated pathologies of the sickle cell patients**

| Variables | Male patients with SCDs* | *p*-value | Female patients with SCDs |
|---|---|---|---|
| Painful crises per year | 5.0 ± 7.1 (0-36) | Ns† | 4.9 ± 8.6 (0-52) |
| ***Transfused units of RBCs‡*** | ***47.6 ± 61.6 (0-434)*** | ***0.000*** | ***28.4 ± 35.8 (0-206)*** |
| ***COPD§*** | ***25.4% (56)*** | ***<0.001*** | ***7.2% (15)*** |
| ***Ileus*** | ***7.2% (16)*** | ***<0.001*** | ***1.4% (3)*** |
| ***Cirrhosis*** | ***7.2% (16)*** | ***<0.001*** | ***1.9% (4)*** |
| ***Leg ulcers*** | ***20.0% (44)*** | ***<0.001*** | ***7.2% (15)*** |
| ***Digital clubbing*** | ***14.0% (31)*** | ***<0.001*** | ***6.2% (13)*** |
| ***CAD¶*** | ***18.1% (40)*** | ***<0.05*** | ***12.9% (27)*** |
| ***CRD**** | ***10.4% (23)*** | ***<0.05*** | ***6.2% (13)*** |
| ***Stroke*** | ***12.2% (27)*** | ***<0.05*** | ***7.6% (16)*** |
| Pulmonary hypertension | 12.7% (28) | Ns | 12.5% (26) |
| Varices | 8.6% (19) | Ns | 5.7% (12) |
| Rheumatic heart disease | 6.8% (15) | Ns | 5.7% (12) |
| Avascular necrosis of bones | 25.0% (55) | Ns | 25.0% (52) |
| Sickle cell retinopathy | 0.9% (2) | Ns | 0.4% (1) |
| Mortality | 7.2% (16) | Ns | 6.7% (14) |

*Sickle cell diseases †Nonsignificant (p>0.05) ‡Red blood cells §Chronic obstructive pulmonary diseases ¶Coronary artery disease **Chronic renal disease

## Discussion

Chronic endothelial damage may be the leading cause of early aging and premature death in human beings. Physical inactivity, excess weight, smoking, alcohol, chronic inflammatory or infectious processes, and cancers may accelerate the process. Probably, it is the most common type of vasculitis all over the world. Whole afferent vasculature including capillaries may mainly be involved in the process. Much higher BP of the afferent vasculature may be the major underlying cause by inducing recurrent injuries on endothelium. Thus the term of venosclerosis is not as famous as atherosclerosis in the literature. Secondary to the permanent endothelial inflammation, edema, and fibrosis, vascular walls become thickened, their lumens are narrowed, and they lose their elastic nature that reduces blood flow and increases systolic BP further. Although early withdrawal of the causative factors may retard the final consequences, after development of HT, DM, cirrhosis, COPD, CRD, CAD, PAD, mesenteric ischemia, osteoporosis, or stroke, endothelial changes cannot be reversed completely due to their fibrotic natures (10).

SCDs are life-threatening hereditary disorders affecting around 100,000 individuals in the United States (11). As a difference from other causes of chronic endothelial damage, the SCDs may keep vascular endothelium particularly at the capillary level (12), because the capillary system is the main distributor of the hard RBCs into the tissues. The hard cells induced severe and permanent endothelial damage, inflammation, edema, and fibrosis terminate with end-organ insufficiencies in early years of life. As a result, mean lifespans of the patients were 48 years in females and 42 years in males in the literature (13), whereas they were 33.3 and 30.8 years in the present study, respectively. The great differences may be secondary to delayed diagnosis, delayed initiation of hydroxyurea therapy, and inadequate RBC supports during medical or surgical emergencies in Hatay region of Turkey. Actually, RBC supports must be given during all medical or surgical emergencies in which there is an evidence of clinical deterioration in the SCDs (14, 15). RBC supports decrease sickle cell concentration in the circulation and suppress bone marrow for the production of abnormal RBCs. So it decreases sickling induced endothelial damage all over the body during such events. According to our 18-year experiences, simple RBC transfusions are superior to the exchange. First of all, preparation of one or two units of RBC suspensions at each time rather than preparation of six units or higher provides time for clinicians to prepare more units by preventing sudden death of such patients. Secondly, transfusion of one or two units of RBC suspensions at each time decreases the severity of pain and relaxes anxiety of the patients and surroundings in a short period of time. Thirdly, transfusions of lesser units of RBC suspensions at each time decrease transfusion-related complications in the future. Fourthly, transfusions of RBC suspensions in the secondary health centers prevent some deaths developed during transport to the tertiary centers for the exchange. Fifthly, transfusions of RBC suspensions in the secondary health centers save some extra costs on the health system incurred during the transport to tertiary centers. On the other hand, longer survival of females in the SCDs (13) and longer overall survival of females in the world (16) cannot be explained by the atherosclerotic effects of smoking and alcohol alone, instead it may be explained by the physical power dependent role of male sex in life that may terminate with an exaggerated sickling and vascular endothelial damage in early years of life (17).

Malignancy is a proliferation of cell with loss of normal controls resulting in unregulated growth, lack of differentiation, local tissue invasion, and metastasis. Although the genetic background of this unregulated cell growth cannot be detected in all cancer types, yet it is highly suspected that this abnormal behavior is caused by a DNA change in the cancer cell since the cell behaves under the control of its genetic material. Mutations of genes are responsible for the excessive proliferation of the malignant cells. These mutations may alter the quantity or behavior of the proteins encoded by growth-regulating genes and accelerate cell division. Oncogenes are abnormal genes that normally regulate cell growth. For instance, the ras gene is abnormal in about 25% of all human cancers (18). Ras protein is encoded by the ras gene, and it signals cancer cells to divide. Another example of the oncogenic activity is protein kinases that are the enzymes regulating several cellular activities. Many cancers contain structurally altered protein kinases. If overproduced or altered, these kinases stimulate cell division, continuously. Tumor suppressor genes normally suppress the development of cancers by encoding proteins. Mutations in the tumor suppressor genes occur in many cancers, allowing affected cells to divide, continuously (19). Another important regulatory protein, p53, prevents replication of damaged DNA, and promotes apoptosis of the cells. Inactive or altered p53 allows cells with abnormal DNA to survive and divide. The p53 gene appears defective in most of the human malignancies (20). The deletion, translocation, or duplication of important genes provides proliferative advantages to cancer cells over the normal cells, and a tumor may develop. Similarly, chromosomes break easily, putting children at high risk of developing cancers in some congenital diseases (21). Viruses can also cause cancers in human beings by integration of the provirus (double-stranded DNA copy of the viral RNA genome) into the cellular genome. For example, HBV accounts for more than 60% of HCC cases (22). Similarly, we detected a case of HCC in the presence of HBsAg positivity in the control group in the present study. Ultraviolet radiation and ionizing radiation are also carcinogenic by means of the DNA damage; for example, survivors of the atomic bomb in Hiroshima and Nagasaki had higher prevalence of several cancers (23). Similarly, when ionizing radiation in the form of x-rays is used to treat nonmalignant diseases including acne and ankylosing spondylitis, prevalence of several cancers increase. Normally, cancers cells with abnormal genetic material may develop in the human body everyday but immune cells, particularly the natural killers, detect and destroy them. The increased prevalence of several types of human cancers with aging may also show the significance of the immune system for the cancer development. The weakened immunity by aging may increase prevalence of cancers and reactivation tuberculosis in the human being (24). Disseminated atherosclerotic process all over the body by aging may also be important for the weakened immunity since immune cells cannot reach end organs of the body (25). So cancer cells proliferate easily since they have some survival advantages over the normal cells secondary to the genetic changes. On the other hand, immunologic activation may be important for the clearance of cancer cells in the body. Similarly, chronic vascular endothelial inflammation of the SCDs initiated at birth may increase clearance of the abnormal cells by the body's own immune cells and decrease prevalence of the malignancies in such patients. The prevalence of malignancies were significantly lower in the SCDs in the present study ($p<0.001$ both for females and males). On the other hand, a strong immune system is also important for the prevention of malignancies since immune cells can destroy the genetically changed cells. For example, patients with immunodeficiency including HIV infection and aging are at higher risk for various cancers. Patients with systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), or Sjögren's syndrome are at higher risk for lymphoma, usually the B-cell type, presumably due to the altered immunologic status of the patients. Similarly, parallel to the lower prevalence of malignancies, we detected significantly lower prevalence of SLE and RA in the SCDs in the previous studies (26, 27).

SCDs are severe inflammatory processes terminating with major health problems in early years of life (28). For example, menarche is retarded in females with the SCDs (4). Additionally, the severe and permanent vascular endothelial inflammation all over the body causes an overlapping chronic disease anemia (29). Furthermore, end-organ insufficiencies can even suppress the immune system of the patients. Sinusitis, tonsillitis, and urinary tract infections are the common causes of painful crises and hospitalizations, and they can rapidly progress into the severe and life-threatening infections including pneumonia, meningitis, and sepsis due to the relative immunosuppression in the SCDs (30). For example, prolonged tonsillary hypertrophy is a common physical examination finding that may be the result of a prolonged infectious process due to the relative immunosuppression in them (31). Severe and permanent endothelial inflammation induced prominent weight loss and cachexia are also common in them (4). Autosplenectomy, painful crises, hospitalizations, invasive procedures, RBC supports, medications, prevented normal daily activities, and an eventually suppressed mood of the body can even suppress the immune system (32, 33). In another definition, SCDs may cause a moderate immunosuppression with several mechanisms in the human body. Although the moderate to severe immunosuppression, the significantly lower prevalence of malignancies in the SCDs may be explained by the permanently activated immune cells on vascular endothelium since such immune cells increase clearance of genetically changed malignant cells all over the body.

As a conclusion, SCDs are chronic and severe inflammatory processes on vascular endothelium initiated at birth, and terminate with end-organ insufficiencies in early years of life. Such permanent inflammatory processes may increase clearance of malignant cells by immune system all over the body which may be the cause of significantly lower prevalence of malignancies in the SCDs.

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# Varicocele may not have a chronic low-grade inflammatory background on vascular endothelium

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## Abstract

Background: There is not enough finding about effects of metabolic parameters on varicocele in the literature.

Methods: Consecutive patients with a surgical repair history of varicocele were collected into the first, and age-matched control cases were collected into the second, groups.

Results: The study included 31 patients with varicocele and 80 control cases, totally. Mean age of varicocele patients was 37.0 years. Interestingly, 77.4% of the varicoceles were on the left side and 9.6% of them were on the right side ($p<0.05$), and 12.9% of them were found bilaterally. When we compared the two groups according to mean weight, height, body mass index, triglyceride, and low density lipoproteins and prevalences of smoking, white coat hypertension, hypertension, diabetes mellitus, and coronary artery disease, there was not any significant difference according to any metabolic parameter in between ($p>0.05$ for all).

Conclusion: Although the metabolic syndrome is a chronic low-grade inflammatory process on vascular endothelium, terminating with an accelerated atherosclerosis, end-organ failure, early aging, and premature death, varicocele may not have a chronic low-grade inflammatory background on vascular endothelium in general. On the other hand, thalassemias and other causes of splenomegaly may cause torsion of the left renal vein and prevent its drainage. So drainage problems at the level of left renal vein due to the stronger arterial walls that cannot be obstructed easily may explain the higher prevalence of varicocele and renal atrophy on the left side in the literature since the left testicular vein drains into the left renal vein.

Key words: Varicocele, endothelial inflammation, metabolic syndrome, body mass index

## Introduction

Due to the prolonged survival of human beings, systemic atherosclerosis may be the major health problem in this century, and its association with sedentary lifestyle, excess weight, smoking, and alcohol is collected under the heading of metabolic syndrome (1, 2). The syndrome is characterized by a chronic low-grade inflammatory process on vascular endothelium in the whole body (3). The inflammatory process is particularly accelerated by some factors including physical inactivity, excess weight, smoking, alcohol, chronic inflammation and infections, and cancers (4, 5). The syndrome can be slowed down with appropriate nonpharmaceutical approaches including lifestyle changes, diet, exercise, cessation of smoking, and withdrawal of alcohol (6). The syndrome contains reversible indicators including overweight, white coat hypertension (WCH), impaired fasting glucose, impaired glucose tolerance, hyperlipoproteinemias, alcohol, and smoking for the development of irreversible consequences including obesity, hypertension (HT), type 2 diabetes mellitus (DM), chronic obstructive pulmonary disease, cirrhosis, chronic renal disease, peripheric artery disease, coronary artery disease (CAD), and stroke (7, 8). In another perspective, the metabolic syndrome may be the most significant disease of human beings decreasing quality and duration of human lifespan at the moment. The syndrome induced accelerated atherosclerotic process in the whole body may be the leading cause of end-organ failure, early aging, and premature death for both genders. For example, CAD is the leading cause of death in developed countries. On the other hand, varicocele is a dilatation of pampiniform venous plexus within the scrotal sac (9-12). It occurs in 15-20% of males and 40% of infertile males, since researchers documented a recurrent pattern of low sperm count, poor motility, and predominance of abnormal sperm forms in varicocele cases (13-15). We tried to understand whether or not there are some significant relationships between metabolic parameters and varicocele in the present study.

## Material and methods

The study was performed in the Internal Medicine Polyclinic of the Mustafa Kemal University between March 2007 and December 2009. Consecutive patients with a surgical repair history of varicocele were collected into the first, and age-matched control cases were collected into the second, groups. Their medical histories including smoking habit, HT, DM, CAD, and already used medications were learnt, and a routine check up procedure including fasting plasma glucose (FPG), triglyceride, low density lipoproteins (LDL), and an electrocardiography was performed. Current daily smokers at least for the last six months, and cases with a history of five pack-years were accepted as smokers. Insulin using diabetics and patients with devastating illnesses including malignancies, acute or chronic renal failure, chronic liver disease, hyper- or hypothyroidism, and heart failure were excluded to avoid their possible effects on weight. Body mass index (BMI) of each individual was calculated by the measurements of the same internist instead of verbal expressions. Weight in kilograms is divided by height in meters squared (16). Office blood pressure (OBP) was checked after a 5 minute rest in seated position with the mercury sphygmomanometer on three visits, and no smoking was permitted during the previous 2 hours. A 10 day twice daily measurement of blood pressure at home (HBP) was obtained in all cases, even in normotensives in the office due to the risk of masked hypertension after a 10 minutes of education about proper blood pressure (BP) measurement techniques (17). The education included recommendation of upper arm while discouraging wrist and finger devices, using a standard adult cuff with bladder sizes of 12 x 26 cm for arm circumferences up to 33 cm in length and a large adult cuff with bladder sizes of 12 x 40 cm for arm circumferences up to 50 cm in length, and taking a rest at least for a period of 5 minutes in the seated position before measurement. A 24 hour ambulatory blood pressure monitoring was not required due to its equal effectiveness with HBP measurements (8). Eventually, HT is defined as a BP of 135/85 mmHg or greater on HBP measurements (17). WCH is defined as OBP of 140/90 mmHg or greater, but mean HBP of lower than 135/85 mmHg, and masked HT as OBP of lower than 140/90 mmHg, but mean HBP of 135/85 mmHg or greater (17). Cases with an overnight FPG level of 126 mg/dL or greater on two occasions or already using antidiabetic medications were defined as diabetics. An oral glucose tolerance test with 75-gram glucose was performed in cases with a FPG level between 100 and 125 mg/dL, and diagnosis of cases with a 2 hour plasma glucose level of 200 mg/dL or higher is DM (16). A stress electrocardiography was performed in suspected cases, and a coronary angiography was obtained only for the stress electrocardiography positive cases. Eventually, mean weight, height, BMI, triglyceride, and LDL values and prevalence of smoking, WCH, HT, DM, and CAD were detected in each group, and results were compared in between. Mann-Whitney U Test, Independent-Samples T Test, and comparison of proportions were used as the methods of statistical analyses.

## Results

The study included 31 patients with varicocele and 80 control cases, totally. Mean age of varicocele patients was 37.0 years. Interestingly, 77.4% of the varicoceles were on the left side and only 9.6% of them were on the right side ($p<0.05$), and 12.9% of them were found, bilaterally. When we compared the two groups according to mean weight, height, BMI, triglyceride, and LDL values and prevalence of smoking, WCH, HT, DM, and CAD, there was not any statistically significant difference according to any metabolic parameter in between ($p>0.05$ for all) (Table 1 - next page).

**Table 1: Characteristic features of the study cases**

| Variables | Cases with varicocele | *p*-value | Control cases |
|---|---|---|---|
| Number | 31 | | 80 |
| ***Mean age (year)*** | ***37.0 ± 12.5 (18-75)*** | Ns* | 38.1 ± 11.1 (19-75) |
| Prevalence of smoking | 61.2% (19) | Ns | 52.5% (42) |
| Mean weight (kg) | 80.0 ± 14.6 (51-99) | Ns | 79.5 ± 12.8 (52-111) |
| Mean height (cm) | 175.0 ± 7.2 (152-187) | Ns | 173.5 ± 7.2 (158-195) |
| Mean BMI† (kg/m2) | 26.0 ± 4.2 (16.6-33.5) | Ns | 26.3 ± 4.0 (18.0-39.2) |
| Mean triglyceride (mg/dL) | 131.0 ± 77.3 (63-332) | Ns | 164.0 ± 81.7 (51-385) |
| Mean LDL‡ (mg/dL) | 127.8 ± 36.1 (66-198) | Ns | 125.8 ± 34.9 (63-208) |
| Prevalence of WCH§ | 35.4% | Ns | 31.2% |
| Prevalence of HT‖ | 3.2% | Ns | 1.2% |
| Prevalence of DM¶ | 0.0% | Ns | 3.7% |
| Prevalence of CAD** | 3.2% | Ns | 0.0% |

*Nonsignificant (p>0.05) †Body mass index ‡Low density lipoproteins §White coat hypertension ‖Hypertension ¶Diabetes mellitus **Coronary artery disease

## Discussion

Probably obesity is found among one of the irreversible endpoints of the metabolic syndrome, since after development of obesity, nonpharmaceutical approaches provide limited benefit either to heal obesity or to prevent its complications. Overweight and obesity probably lead to a chronic low-grade inflammation on vascular endothelium that is associated with many coagulation and fibrinolytic abnormalities suggesting that excess weight may cause a prothrombotic and proinflammatory state all over the body (18). The chronic inflammatory process is characterized by lipid-induced injury, invasion of macrophages, proliferation of smooth muscle cells, endothelial dysfunction, and increased atherogenicity (19, 20). Elevation of C-reactive protein (CRP) levels in serum carries predictive power for the development of atherosclerotic end-points (21, 22), and overweight and obesity are considered as strong factors for controlling of CRP concentration in serum, because adipose tissue produces biologically active leptin, tumor necrosis factor-alpha, plasminogen activator inhibitor-1, and adiponectin. So adipose tissue is involved in the regulation of cytokines, and individuals with overweight and obesity have increased CRP levels in serum (23, 24). On the other hand, individuals with excess weight will have an increased circulating blood volume as well as an increased cardiac output, thought to be the result of increased oxygen need of the extra tissue. The prolonged increase in circulating blood volume may cause myocardial hypertrophy and decreased compliance, in addition to the common comorbidity of atherosclerosis and HT. In addition to atherosclerosis and HT, FPG and total cholesterol levels in serum were elevated parallel to the increased BMI values (25). Similarly, prevalence of CAD and ischemic stroke increased parallel to increased BMI values in another study (26). On the other hand, the chronic low-grade inflammatory process may also cause genetic changes on the epithelial cells, and the systemic atherosclerotic process may decrease clearance of malignant cells by the immune system, effectively (27). Eventually, the risk of death from all causes including cardiovascular diseases and cancers increased throughout the range of moderate to severe weight excess for both genders in all age groups (28).

Testes are paired male genital organs located in the scrotal sac. They contain sperm, spermatogonia (sperm producing cells), Sertoli cells (sperm nourishing cells), and Leydig cells (testosterone producing cells). Epididymis is a small tubular structure attached to the testes that serves as a storage reservoir wherein sperm mature. Sperm travel through the vas deferens, which connects epididymis to the prostate gland. Spermatic cord contains vas deferens, arteries, and veins that are also called pampiniform venous plexus, nerves, and lymphatics. Pampiniform venous plexus drains blood from testes, epididymis, and vas deferens, and eventually become spermatic veins that drain into the main circulation of kidneys. Pampiniform venous plexus may become tortuous and dilated, like varicose veins of legs. So a scrotal varicocele is simply a varicose dilatation of the pampiniform plexus above and around the testicle. As also detected in the present study, varicoceles are much more common on the left side (nearly 80% to 90%) due to several anatomic factors including angle at which the left testicular vein enters the left renal vein, lack of effective

antireflux valves at the juncture of left testicular vein and left renal vein, the nutcracker syndrome, and some other left renal vein anomalies such as passage behind the aorta (29, 30). The nutcracker syndrome results mostly from the compression of the left renal vein between the abdominal aorta and superior mesenteric artery, although some other variants exist (31). But according to our opinion, the higher prevalence of varicocele on the left side may mainly be a result of high prevalence of thalassemia minor and other causes of splenomegaly in the population that may cause drainage problems at the level of left renal vein.

The accelerated atherosclerotic process can also affect the renal arteries, and may lead to poor perfusion of the kidneys leading to renal failure. The right renal artery is longer than the left because of the location of the aorta. Additionally, the right renal artery is lower than the left because of the position of the right kidney. So the left kidney possibly has a relatively higher arterial pressure due to the shorter distance to the heart as an underlying cause of endothelial damage and atherosclerosis. But according to our opinion, the accelerated atherosclerotic process alone cannot explain the significantly higher prevalence of renal atrophy on the left side in the literature (1.3% versus 0.2%, $p<0.001$) (32). On the other hand, the high prevalence of associated thalassemias (30.3%) and splenomegaly (51.5%) with the left renal atrophy cases may be important for the explanation (32), since spleen and left kidney are closely related organs which may also be observed with the development of varicose veins from the left renal vein at the splenic hilus in cirrhotic patients. Any pressure on the left kidney as in splenomegaly cases, may cause torsion of the left renal vein, and prevents its drainage. We especially think about the drainage problems at the level of left renal vein due to the stronger arterial walls that cannot be obstructed easily and the higher prevalences of both renal atrophy and varicocele on the left side in the literature (11, 32).

A patient with varicocele is usually asymptomatic and often seeks an evaluation for infertility after failed attempts at conception. An untreated varicocele, especially if large enough, may cause long-term deterioration in sperm and even testosterone production. But presence of a varicocele does not mean that surgical repair is always required. Young men with varicocele but normal ipsilateral testicular volume should be offered follow-up monitoring with annual objective measurements of testicular volume and semen analyses, since one-sided varicoceles can often affect the opposite testicle (9-12). A previous study suggested that up to 80% of men with a left clinical varicocele had bilateral varicoceles revealed by noninvasive radiologic testing (33). Similarly, 16% of varicoceles in patients with infertility were reported with bilateral occurrence in all of them (15). Reasons for surgical repair include testicular pain unresponsive to symptomatic treatment, testicular atrophy (volume less than 20 mL or length less than 4 cm), and unexplained infertility in males. If an infertile male has bilateral varicoceles, both should be repaired since scrotal varicoceles may be the most common cause of poor sperm production and decreased semen quality. But how varicoceles impair sperm structure, function, and production is unknown. Although an increased heat effect caused by impaired circulation appears to be the most reproducible defect, the possible effects of pressure, oxygen deprivation, and toxins may also be responsible. But regardless of the mechanism of action, varicoceles are a significant factor in decreasing testicular function and reducing semen quality in a large percentage of infertile men.

As a conclusion, although the metabolic syndrome is a chronic low-grade inflammatory process on vascular endothelium, terminating with an accelerated atherosclerosis, end-organ failure, early aging, and premature death, varicocele may not have a chronic low-grade inflammatory background on vascular endothelium in general. On the other hand, thalassemias and other causes of splenomegaly may cause torsion of the left renal vein and prevent its drainage. So drainage problems at the level of left renal vein due to the stronger arterial walls that cannot be obstructed easily, may explain the higher prevalence of varicocele and renal atrophy on the left side in the literature since the left testicular vein drains into the left renal vein.

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# Neural Processing of Food Stimuli in Self-Regulation Brain Regions using Bayesian General Linear Modeling Approach

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## Abstract

Background: One of the social concepts is self-regulation; the ability to regulate and control our thoughts, emotions and behaviors. With developments in neuroscience, the neural understanding of self-regulation has been increased. Weight management is a typical kind of self-regulation which leads to behavioral changes. Also in recent years, investigators have used functional Magnetic Resonance Imaging (fMRI) technique for assessing effects of different stimuli such as food on brain responses. The aim of the current study is to localize self-regulation areas in response to palatable food using a Bayesian Generalized Linear Model (GLM) approach.

Methods: A new proposed Bayesian approach was applied for assessing functional response to palatable food stimuli in a block design of fMRI data with 370 scans of one healthy woman. Regions of Interest (ROIs) including the dorsolateral and medial prefrontal cortex, the inferior frontal gyrus and the mid-ventrolateral frontal cortex were investigated. In this Bayesian approach, Stochastic Partial Differential Equation (SPDE) prior was considered for spatial dependency and AR(1) process was used for temporal correlation via pre-weighting residuals. Finally, inferences were conducted using fast Integrated Nested Laplace Approximation (INLA) approximation.

Results: The results of the present study revealed that palatable food as compared to non-food images elicit stronger activation in brain self-regulation areas including the dorsolateral and medial prefrontal cortex, the inferior frontal gyrus and the mid-ventrolateral frontal cortex.

Conclusion: Self-regulation areas of brain of people who are concerned about their weight, will be activated in confrontation with palatable foods.

Key words SPDE, INLA, fMRI,
Self-regulation regions, Food stimuli

## Introduction

In the past two decades, functional Magnetic Resonance Imaging (fMRI) has become a valuable technology which has been widely used to study the human brain's mechanism in response to experimental stimuli for eliciting visual, auditory or advanced cognitive activities using detection of changes in the flow rate and blood oxygen saturation level(1).

One of the social cognitive concepts is self-regulation; the ability to regulate and control our thoughts, emotions and behaviors. Eating is typical kind of self-regulation and involves one's ability to change dietary behaviors to lose or gain weight and become healthier(2).

Recent developments in neuroscience have increased the neural understanding of self-regulation(3). Because of the availability of poor quality and calorie-dense fast food, the prevalence of overweight and obesity has raised research on food and dietary habits are becoming important issues. Many people are concerned about their weight so limit their food intake in order to avoid weight gain. The conflict between the appeal of palatable foods and weight management leads to self-regulation.

If an individual can self-regulate his or her eating behavior successfully, then change can take place, which can lead to obtaining the intended goal. The defensive self-regulation system of people who are conscious about their weight automatically becomes active in confrontation with palatable foods so leads to maintenance of weight management goals (4).

Also in recent years, investigators have used fMRI techniques for assessing effects of different stimuli such as food on brain responses(5). However, fMRI data have special characteristics: spatial correlation between thousands of variables named voxels and temporal correlations at hundreds of time points at each voxel leads to massive amounts of highly complex data so in addition to statistical modeling of fMRI data that considers both spatial and temporal structures, the computational cost dealing with analysis of such high dimensional data will be challenging. Because of disability of classical Generalized Linear Model (GLM) in considering fMRI data properties, some alternatives such as Bayesian approaches have been proposed(6, 7).

In a Bayesian GLM, specific prior distributions are assumed for the task activation and other unknown parameters in the model, considering them with the likelihood, compose a Bayesian hierarchical model.

Owing to a large amount of data, standard Markov Chain Monte Carlo (MCMC) methods are typically too time-consuming so a recently developed Bayesian inference tool based on integrated nested Laplace approximation (INLA) has been employed(8). INLA method can compute approximations to the posterior distributions and manage large data sets in a shorter time by using the sparsity of Gaussian Markov Random Fields (GMRFs). Also INLA is much faster than MCMC (9) and can be easily implemented using R-INLA package(10).

The present study uses fMRI data to identify self-regulation areas reactive to palatable food stimuli. A new proposed Bayesian GLM approach is applied for statistical analysis.

Predetermined self-regulation areas in recent studies include some regions in the prefrontal cortex (PFC) so response to food images will be assessed in these parts of the human brain (11-13).

## Materials and Methods

**1. Subjects**

In a block experiment, thirty healthy, normal weight, right handed women with mean age of 22.1 years performed a passive viewing task with blocks of food and non-food images. For our aim in this research the first subject was selected. The fMRI data used in this study was downloaded from the OpenfMRI database. Its accession number is ds000157 (4).

**2. Stimuli**

During scanning, subjects alternatively viewed 16 blocks of food and non-food images (i.e., office utensils), with 8-16 seconds rest blocks. Halfway the task, there was 10 seconds break. 8 images were presented for 2.5 seconds each with 0.5 seconds inter-stimulus interval in the image blocks. All pictures were food objects on a white background.

**3. Functional Magnetic Resonance Imaging**

The functional scan was a T2 weighted gradient echo 2D-echo planar imaging sequence (64×64, repetition time=1600 ms, echo time=23 ms, flip angle=72.5, FOV=208×119×256 mm, SENSE factor AP=2.4, 30 axial 3.6 mm slices with 0.4 mm gap, reconstructed voxel size=4×4×4 mm).

In one functional run 370 scans were obtained which lasted 10 minutes. In addition to functional data, a high resolution T1-weighted anatomical MRI scan was made (3D gradient echo sequence, repetition time=8.4 ms, echo time=3.8 ms, flip angle=8, FOV=288×288×175, 175 sagittal slices, voxel size=1×1×1mm).

**4. Data processing and statistical analysis**

The data was pre-processed with regard to pipeline in Smeet et al and using SPM12 software package (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/), which includes removal of spatial distortions, motion realignment, distortion correction, alignment to the structural image, bias field correction and intensity normalization(14); also Gaussian filter with 8 mm FWHM was used to smooth the images, high pass filtering was done with cutoff 128 s. These are standard steps in fMRI data preprocessing and are necessary to align the data into a common space and remove main sources of noise.

Design matrix was generated by fitting a boxcar function to each time series convolved with canonical hemodynamic response function.

**5. Statistical analysis**

New proposed method by Mejia in 2017 was applied to perform statistical inferences(10).

Consider the following GLM:

$$\mathbf{y}=\sum_{k=0}^{K}\mathbf{X}_k\boldsymbol{\beta}_k+\sum_{j=1}^{J}\mathbf{Z}_j\mathbf{b}_j+\boldsymbol{\varepsilon} \quad \varepsilon \sim N(0,V) \quad (1)$$

Here y is a TN ×1 vector containing the fMRI time series of all voxels, and the $X_k$ and $Z_j$ are TN ×N design matrices for the activation amplitudes $\beta_k$ (including baseline $\beta_0$) and nuisance signals $b_j$, respectively. The matrix V is a T×T covariance matrix for an AR(p) process, where p is the degree of autoregressive.

To account for spatial correlation, spatial prior on each $\beta_k$ for k = 0, … , K was considered, where K is number of tasks under investigation. One of the popular spatial structures is the class of Matérn Gaussian fields that have flexible covariance function between locations. We say $\beta(u)$ is a Matérn Gaussian process if the covariance between u and v $(u, v \in \mathbb{R}^d)$ is given by

$$Cov(u,v)=\frac{\sigma^2}{2^{\nu-1}\Gamma(\nu)}(\kappa\|u-v\|)^{\nu}K_{\nu}(\kappa\|u-v\|) \quad (2)$$

Where $K_\nu(.)$ is the modified Bessel function of the second kind with order $\nu > 0$, $\Gamma(.)$, is the gamma function, $K > 0$ is the spatial scale, and $\sigma^2 > 0$ is the variance.

However, covariance matrix of Matérn spatial process is dense so its inverse is difficult and is not computationally possible for big data sets. This problem has been addressed by solving the stochastic partial differential equation (SPDE) and obtaining an explicit GMRF representation for Matérn Gaussian fields (15).

Here, the steps of INLA-SPDE are briefly described as follows.

1) The non-convex hull meshes using coordinates of voxels was constructed. The spatial correlation structure for the SPDE part of the model was defined by the meshes. Herein, the Constrained Refined Delaunay Triangulation was made with the “inla. mesh.2d” function.

2) A projection matrix was calculated. Because the SPDE model was defined on the mesh, the process at the mesh vertices is required to be projected to the locations response. Details about the calculation of the projector matrix can be found in Lindgren et al. (16).

3) The SPDE model based on the constructed meshes in step 1 was defined. Here the Matérn correlation function was applied which was available in R-INLA.

4) A hierarchical model was specified using equation (1) according to Krainski et al (17). The hierarchical model implemented in INLA-SPDE includes three components (i.e. intercept, the fixed effect, and random effect). In this study, each stimulus was considered as random effects. Then the Normal family was considered for probability distribution of the response.

5) Finally, the posterior distribution of the parameters was estimated.

For more details about SPDE and INLA method refer to Blangiardo et al (18).

To consider temporal correlation of time series and to reduce the computational cost of fitting the Bayesian model, the fMRI time courses were first pre-whitened by assuming an AR (1) process on the residuals from a classical GLM with uncorrelated errors.

Pre-whitened steps are done as below.
(1) The p AR coefficients for each location in the brain were estimated.

(2) The pre-whitening matrix W for each location in the brain was computed resulting in N T×T matrices, where N is the number of voxels in the brain.

(3) Finally, the regression model Wy = WXβ + Wε was fit at each voxel to get estimates and standard errors for β for each subject and voxel.

To account for noise due to subject motion, six rigid body realignment parameters that were estimated in the motion realignment stage of preprocessing were included in the model as nuisance covariates. Furthermore, linear and quadratic time terms were included for considering scanner drift.

In this study, a Regions of Interest (ROIs) analysis was conducted focusing on the dorsolateral and medial prefrontal cortex, the inferior frontal gyrus and the mid-ventrolateral frontal cortex.

The mask of the selected regions was made using the WFU PickAtlas toolbox in MATLAB R2016b software(19). All brain images were mapped to Type 2 Eve Atlas of the SPM12 (20). Data are prepared by programming in MATLAB R2016b software and then model fitting is performed using R-INLA package (http://www.r-inla.org).

## Results

In brain anatomy, PFC is the cerebral cortex which covers the front part of the frontal lobe. Subdivision parts of the prefrontal cortex based on Brodmann areas are mentioned in Table 1. From these regions, the dorsolateral and medial prefrontal cortex (BA9), the inferior frontal gyrus (BA45) and the mid-ventrolateral frontal cortex (BA47) were chosen for analysis. These regions are shown in Figure 1.

| Prefrontal cortex | Brodmann areas |
|---|---|
| Lateral (Dorsolateral, Ventrolateral) | 9, 46, 12, 44, 45, 47 |
| Medial | 9,10,24,25,32 |
| Orbitofrontal | 11,13,14 |
| Caudal | 8 |

**Table 1: subdivision parts of the prefrontal cortex based on Brodmann areas**

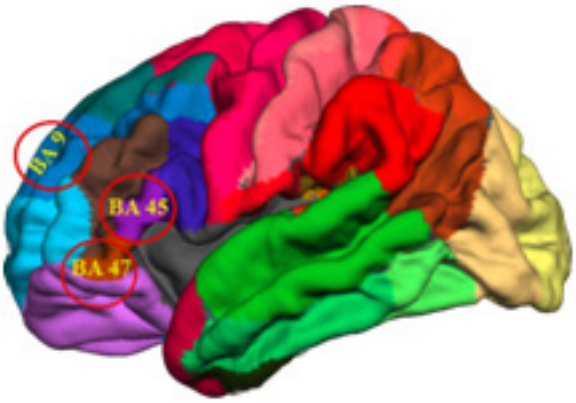


**Figure 1: ROIs in present study based on Brodmann area atlas**

Activation of mentioned areas in response to palatable food versus non-food stimuli was examined using Bayesian GLM model. The results of fitted model are illustrated as figures.

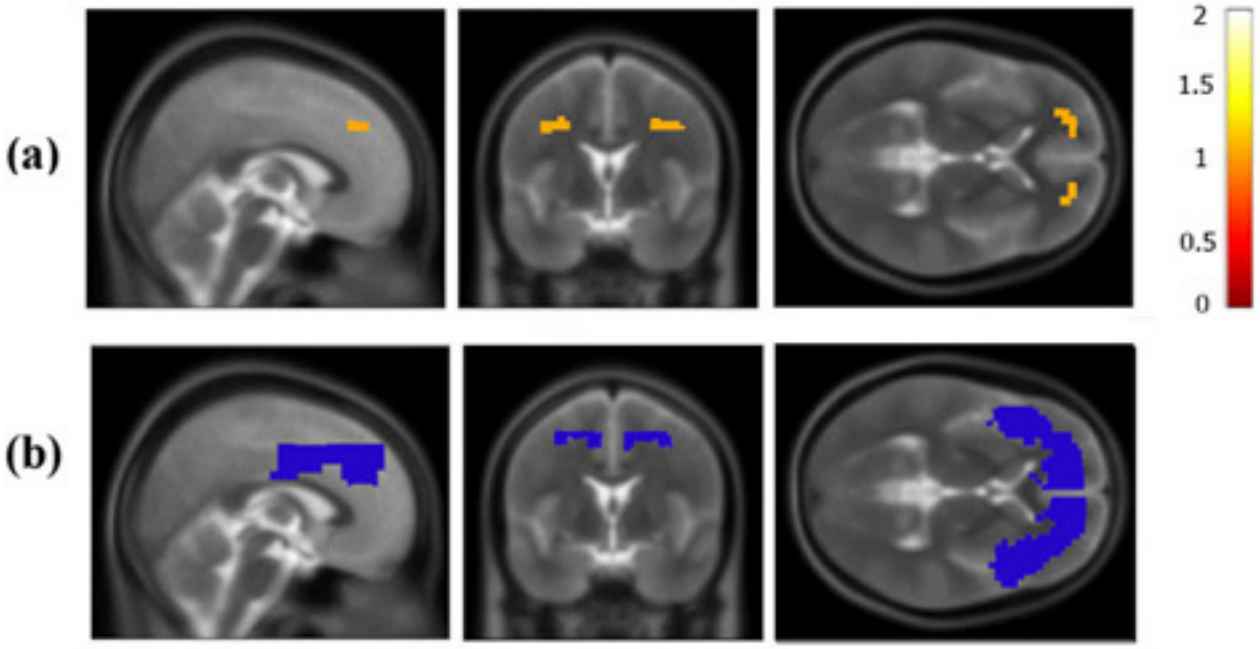


**Figure 2: a) Brain regions with stronger activation in response to palatable food vs non-food images. b) The mask of dorsolateral and medial prefrontal cortex**

Figure 2a displays the posterior mean of palatable food versus non-food images for the dorsolateral and medial prefrontal cortex in three different views: Sagittal, Coronal and Axial. The dorsolateral and medial prefrontal cortex were stronger activated during viewing of palatable food images.

The white and yellow colors indicate the stronger activation and the orange and red colors represent a weaker and zero activation, respectively. Figure 2b is the mask of the dorsolateral and medial prefrontal cortex and the voxels of this region are displayed in blue.

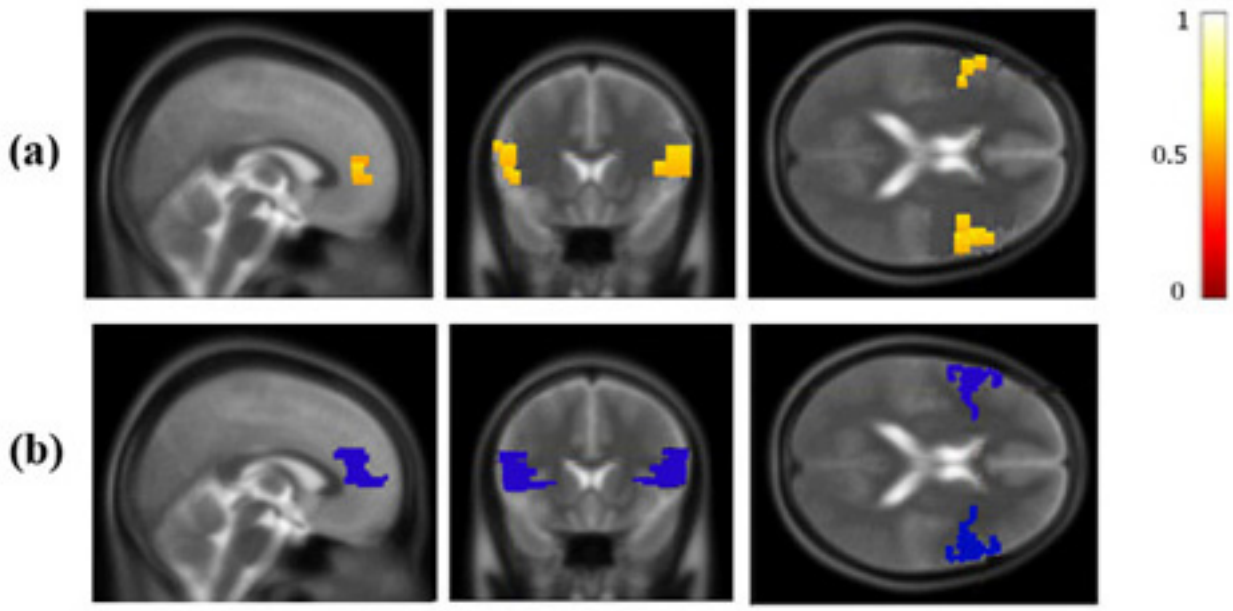


**Figure 3: a) Brain regions with stronger activation in response to palatable food vs non-food images b) The mask of inferior frontal gyrus**

Figure 3a displays the posterior mean of palatable food versus non-food images for the inferior frontal gyrus in three different views: Sagittal, Coronal and Axial. The inferior frontal gyrus was stronger activated during viewing of palatable food images.

The white and yellow colors indicate the stronger activation and the orange and red colors represent a weaker and zero activation, respectively. Figure 3b is the mask of the inferior frontal gyrus and the voxels of this region are displayed in blue.

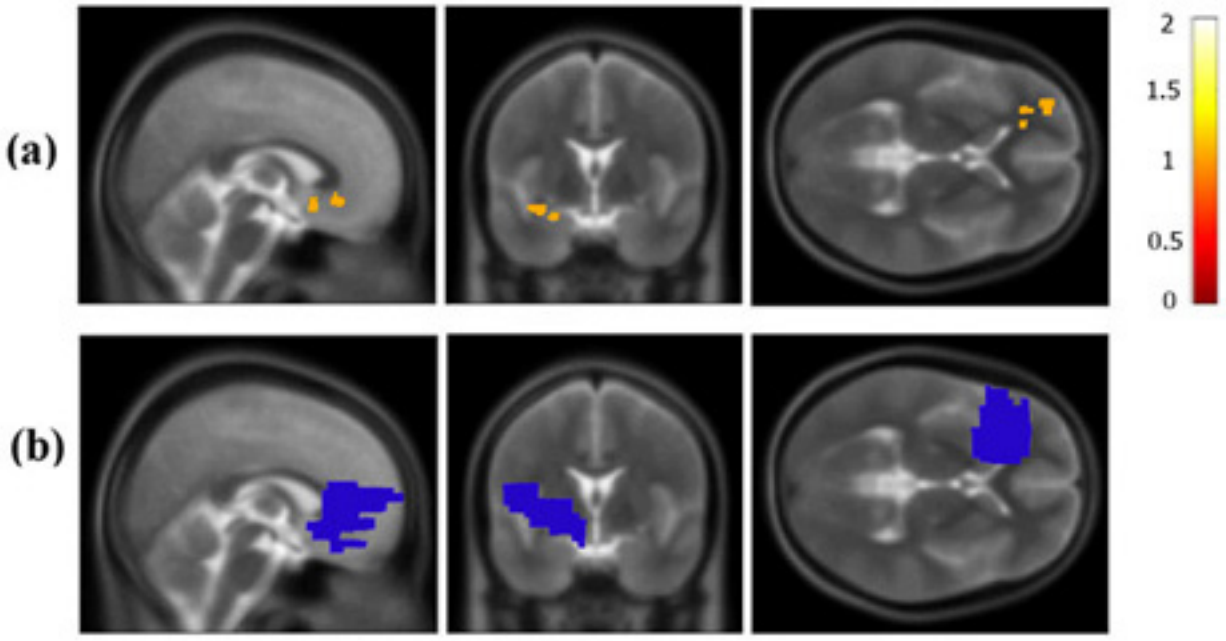


**Figure 4: a) Brain regions with stronger activation in response to palatable food vs non-food images b) The mask of mid ventrolateral frontal cortex**

Figure 4a displays the posterior mean of palatable food versus non-food images for the mid-ventrolateral frontal cortex in three different views: Sagittal, Coronal and Axial. The mid-ventrolateral frontal cortex elicited stronger activation during viewing of palatable food images.

The white and yellow colors indicate the stronger activation and the orange and red colors represent a weaker and zero activation, respectively. Figure 4b is the mask of the mid-ventrolateral frontal cortex and the voxels of this region are displayed in blue.

## Discussion

One of the important aspects of human behavior is self-regulation which has been studied through the social aspect and personality psychology as well as cognitive psychology(21). Recent progressions in neuroscience have led to understanding the neural foundations of self-regulation. Weight management is a typical kind of self-regulation which leads to behavioral changes. Based on prior studies, prefrontal cortex is one of the most effective regions in the self-regulation cognitive function.

In the present research, INLA-SPDE approach was applied for assessing functional response to palatable food images in a block design fMRI data. The areas including the dorsolateral and medial prefrontal cortex, the inferior frontal gyrus and the mid-ventrolateral frontal cortex were considered. Using the described Bayesian approach, the mentioned regions in the frontal cortex elicited stronger activation during palatable food versus non-food images and our results were similar to previous studies. The results showed that self-regulation areas will be activated in people who are concerned about their weight. The results showed the self-regulation areas of people who are concerned about their weight will be activated in confrontation with palatable foods.

The results of previous studies showed that various cortical regions have been involved in self-regulation of which the prefrontal cortex is most notable for cognitive processes that are implicated in self-regulation(22-24). The three main areas of PFC particularly important to self-regulatory functioning are ventromedial PFC (vMPFC) including orbitofrontal cortex, lateral PFC, and the anterior cingulate cortex (ACC)(3, 25). Smeets et al addressed brain activation of self-regulation in response to food cues using fMRI technique. They concluded the activation of self-regulation areas in response to food cues will be adjusted by the importance of weight management goal. They used ROIs: the lateral prefrontal cortex, inferior frontal gyrus and the anterior cingulate cortex and observed activation in these areas(4). Charbonnier et al examined brain responses during food choices between equally liked high and low calorie foods. Food choice compared to non-food choice evoked stronger activation in the left insula, superior temporal sulcus, posterior cingulate gyrus and (pre) cuneus(26). Huerta et al conducted a meta-analysis of neural responses to visual food cues. They showed that regions that lay within the visual system proper (occipital lobe) have significant activations. The most robust activation convergence was in the right fusiform gyrus. Lateralized convergent activations were observed in the left insula, right postcentral gyrus, right precuneus, left inferior frontal gyrus, left middle occipital gyrus and left hippocampus. Bilateral convergent activations were seen in the fusiform gyrus, declive, parahippocampus and superior temporal gyrus(27).

A new Bayesian GLM approach was proposed and applied on cortical surface fMRI data from the Human Connectome Project (HCP). They mapped the volumetric fMRI data to the cortical surface manifold then used INLA for computational approximation(10).

In this study, INLA-SPDE approach was used for analysis of volumetric fMRI data. Most of the Bayesian methods for volumetric fMRI reduce computational trouble by using variational Bayes(VB); however, VB underestimates posterior variance so INLA approach was used as in the study of Mejia et al. INLA is a computationally efficient but highly accurate approximation Bayesian inference tool. Since INLA is less computationally demanding than MCMC, it gave the researchers capability of fitting a complex model based on flexible SPDE spatial processes in order to consider spatial correlation of voxels appropriately.

In this study, we considered only some areas in PFC, one can assess whole brain in response to food stimuli to find more related regions. Also, single subject analysis was conducted in the current research, for future works group analysis could be considered using multi subject Bayesian GLM approach proposed by Mejia et al. Based on literature, the genetic and environmental factors influence on self-regulation's development, so in addition to fMRI data, by collecting genetic information from this experiment, additional research could be done to assess the self-regulation cognitive process by considering and modifying genetic factors.

## Conclusion

In conclusion, increased activations were observed in dorsolateral and medial prefrontal cortex, the inferior frontal gyrus and the mid-ventrolateral frontal cortex during viewing of palatable food versus non-food images. This suggests that self-regulation areas of people who are concerned about their weight, will be activated in confrontation with palatable foods. Although in the present study fMRI is used as a tool to study weight management, one of the goals will be to extend this research into the clinical area, such as developing pharmacological treatments for obesity, by means of assessing the fMRI response to administration of new drugs in obese populations.

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# Surgical Skills Series - Ingrown toenail removal with phenol

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## Introduction

Left to right: Surgeons Mr. Maurice Brygel and Mr. Charles Leinkram

This is the first of an Instructive series on surgical skills for General Practitioners / Family Physicians and Surgical students.

# INGROWN TOENAIL TREATMENT - Conservative, Nail Edge Removal, with Phenol & Wedge Resection treatment

**Figure 1: Ingrown toenail showing nail edge digging into skin and causing bleeding and inflammation**

This painful condition mainly affects the big toe on one or both sides . The nail edge grows into and irritates the overlying skin. An infection may then supervene. The pain or infection may continue to recur unless the cause is permanently removed.

This condition is most common in males, then female teenagers but can occur at any age. Possibly tight footwear, sweaty socks, the foot growing rapidly, all contribute. This combined with incorrect trimming of the nail, results in a spike from the nail edge burrowing into the overhanging skin causing irritation ,pain and infection. In older patients particularly, underlying conditions such as diabetes, poor blood supply, fungal disease or trauma may also be factors.

Occasionally other toes may be effected.

**Conservative Treatment Of Ingrowing Toenails**
There are a multitude of methods including massaging the skin fold away from the nail edge with a cotton bud and elevating the nail edge with a cotton or gauze pledget. Many mistakenly trim the nail edge down whereas it should be trimmed transversely and elevated.Despite this the problem may persist causing pain and infection.

**Operative Treatment For Ingrowing Toenail**
Continuing pain or infection may be indications for surgery. Antibiotics for infection may give only temporary relief as the underlying cause is not removed. When conservative methods are not satisfactory surgical intervention is advised.

Possible risks will also be discussed. It is rare to have any severe problems.

Females may be concerned that the nail could appear narrower.

Before the procedure the patient is given post operative instructions and the costs explained

**Removal Of The Nail Edge**
In the more urgent situation with severe infection just removal of the nail edge under a local anaesthetic nerve block will help overcome the infection. This may give permanent relief in up to 50% if the nail is cared for appropriately following the procedure. However the problem may recur.

**The Use Of Phenol**
This technique still requires a nerve block and removal of the nail edge surgically. It can be done without actually cutting any skin.

It is simpler to perform than a wedge resection particularly for the less experienced.

The phenol is acidic and care has to be taken not to burn the adjacent skin.

There may be less post operative pain than wedge resection.

Should recurrence occur then wedge resection can be performed.

There is possibly a higher rate of recurrence and a higher post operative infection rate.

**Wedge Resection**
Thus, it is recommended by most surgeons for a permanent cure, to perform an operation titled “Wedge Resection”. This removes permanently the nail edge and the corresponding nail bed called the germinal matrix.The nail grows from this matrix.

There may be some pain following this for a day or two.

It means the nail will be permanently a little narrower. Seldomly the nail may fall off or be deformed. This is more likely if there is also a diseased nail.

**The Procedure may be done at a First Visit.**
The patient should be advised to be accompanied by a driver and have transport home, They should also be given information regarding costs. If there is a specific medical condition or they are the fearful fainting type this should be mentioned. You should also obtaion a full medical history includingmedications, previous operations etc to assess their suitability for the procedure .

**Anaesthesia:**
Wedge resection is usually performed under Local Anaesthesia and is termed “a digital block” in the office. Hospitalization or a general anaesthetic is seldom required.

The Local Anaesthetic is injected into each side of the base of the toe. This may sting but is usually tolerated well. The injection takes a few minutes to take effect. The patient can just relax and talk or read whilst waiting. The toe goes numb but does not completely lose the sensation to touch. The effectiveness is tested prior to proceeding. Occasionally an extra injection is required as onset may be slower when there is an infection present. There is no pain during the procedure.

**The Operation:**
A rubber band tourniquet is placed around the base of the toe to prevent bleeding during the procedure . The operation itself only takes a few minutes. One or both sides of the same toe may be treated. Suturing is not required.

**The Bandage:**
The toe is dressed with a non-sticking paraffin gauze (making the dressing easier to change). Dry gauze and a crepe bandage are then applied firmly to prevent bleeding overnight.

The surgeon checks the circulation in the toe to ensure that the bandage is not too tight. The patient is able to walk on theirr heel and be driven home but should not drive. The patient should be given a bootie to wear for cleanliness

**Antibiotics:**
If antibiotics have been commenced, the course should be continued to gain maximum effect. Antibiotics however, are not usually prescribed at the time of operation because removal of the causative nail edge is effective.

The Foot is to be elevated both in the car and on arrival home.

This prevents bleeding and also reduces any throbbing. Occasionally blood seeps through the bandage. Should this occur the foot should be elevated and pressure applied with a towel.

Pain killers such as paracetamol and a codeine are used Panadol, Panadeine or Panadeine Forte, are usually sufficient. Sometimes there is some throbbing pain at night but by the next day this usually subsides. If there is intense pain on the night of the procedure, the bandage can be loosened. The following day the patient is able to walk around on their heel quite freely. They must not get the bandage wet.

**Review:**
The patient should call the surgeon the following day on the number provided. This confirms that all has gone well and there is no need for any urgent appointment.

They should be reviewed 2-3 days following the procedure when the dressing is changed. This can cause some slight discomfort, so a simple pain killer Panadol or Panadeine can be taken ½ hour before arrival at the office. To remove the dressing, the bandage is soaked off. There are no stitches to be removed. Following this a light dressing is applied and is usually reviewed again in a few days time.

The patient should be given instructions on how to treat the nail. Whilst the wound is still healing, and not completely dry, it is better covered with a bandaid rather than have sweaty socks rubbing against it. A shoe cannot be worn for 3-4 days.

It is unusual for recurrence or another infection to occur. If tiny remnants of nail are left free this can be a source of recurring discharge.

**Nail Care:**
The nail is trimmed transversely instead of the into the skin. As the nail grows the edges should be regularly elevated using a cotton bud as should be demonstrated to the patient.

**Conclusion**
Ingrown toenails are not a serious condition. They can however be quite painful and disabling.Usually surgical treatment is successful. The use of Local Anaesthetic makes the procedure comparatively simple.There is a small risk of the problem recurring - possibly 4-10%

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