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EDITORIAL

Dear esteemed readers of TurkJEM Family,

The Society of Endocrinology and Metabolism of Turkey’s “Turkish Journal of Endocrinology and Metabolism” (TurkJEM) is celebrating its twentieth birthday. Throughout this journey a great legacy and input of the academia, stakeholders and members has to be recognized & appreciated. TurkJEM concentrates on clinical, experimental endocrinology and metabolic disorders, published quarterly with a peer review system that esteems recognition. Publication is in English towards endocrinology specialists and practitioner medical doctors. TurkJEM is indexed by the following groups. Throughout its twenty year journey within the world of international academia our journal has become more and more recognized. Presently our journal has become recognized and sourced by; Emerging Sources of Citation Index (ESCI), British Library, CINAHL, Directory of open Access Journals (DOAJ), EBSCO, EMBASE, SCOPUS, ProQuest, Tübitak/Ulakbim TR Index, TurkMedline and Turkiye Citation Index. We have integrated with "Turkish Clinics Automation System from the very beginning of May 2017.

TurkJEM has a very rigorous review system which starts with pre evaluation for ithenticate analysis. Publications having less than 20% ithenticate similarity is sent to editors. The “blind review” process is conducted by two editors is evaluated statistically. Publications receiving an approval will be sent to editors and staff for proof reading. Articles receiving a page format and a DOI number will be published on our website as well. The journal’s excellent team with its rigorous workload manages to execute the total review process in less that two months.

With this professional and occupational dedication our first priority is to be indexed under PubMed framework. Receiving the necessary national and international citation our focus will be indexed by SCI-E. To achieve the proposed vision we have to work in collaboration with you devoted contributors. Knowing and appreciating your work load, we ask for more efforts towards submitting more original articles. In order to promote our new agenda we have organized an “Award Winning Article Contest” with hope of institutionalizing the contest for the years to come. Towards the PubMed efforts we will not accept case reports for publication but will publish the already accepted ones.

The following is the contents of articles for the new issue. Awareness Of Diabetes And Obesity In Turkey; Subclinical Hypothyroidism Is Associated With Atherogenic Lipid Profile In Postmenopausis; Aetiology Of Spontaneous Hypoglycaemia In A South African Hospital ; Hyperglaemia In Hospital: Diagnosis, Classification, Clinical Implications And Treatment ; Genetics Of Type 2 Diabetes Mellitus- Asian Perspective; 5-Alpaha-Reductase deficiency: A review of five cases diagnosed with ambiguous genitalia.

Now that the spring is here, a renewal towards improvement will be our primary agenda. On behalf of TurkJEM I wish you the best that spring can offer.

With my best regards,

Nilgün Başkal MD
Editor-in-Chief
Awareness of Diabetes and Obesity in Turkey
Türkiye’de Diyabet ve Obezite Farkındalığı

Nevin Dinççağ, Selçin Çelik, Cemile İdiz, Yıldız Tütüncü, Sevda Özel Yıldız*, İlhan Satman
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Abstract

Purpose: Diabetes mellitus (DM) and obesity (OB) are rising problems globally, and are also rapidly growing health issues in Turkey. The lack of a proper public awareness has worsened the situation, thereby hampering the implementation of preventive measures. The aim of the present study was to evaluate a questionnaire, specifically designed for measuring the level of awareness of the general Turkish population on DM and OB.

Material and Method: The International Diabetes Federation (IDF) questionnaire was modified to measure the influence of knowledge about diet and physical activity on DM and OB among the Turkish population. We investigated the relationship between the level of knowledge of volunteers on DM and OB and other factors, such as age, gender, socioeconomic status (SES), education, and having DM or a family history of DM. The results were analyzed appropriately using Student’s t-test, Mann–Whitney U test, Kruskal–Wallis test, One-way analysis of variance (ANOVA), and multiple logistic regression model. The present study was observational and designed prospectively.

Results: According to the observations, only 30.1% of the total volunteers that took part in the study had an awareness of DM and OB. There was no statistical difference on the level of knowledge about DM and OB between the various gender groups included in the study (p=0.590). The participants with university level education scored the highest. The mean scores of knowledge on DB and OB were found to be lowest among the people with low SES; however, surprisingly, people with high/very high SES also scored low.

Discussion: The results obtained indicated that the level of awareness of DM and OB was moderate and insufficient. DM and OB were present in approximately 6.5 and 15.2 million people in Turkey, respectively. With a diminished awareness among the Turkish people on DM and OB, the responsibility lies on the shoulders of the young population to create awareness on a large scale for the betterment of the future generations.

Keywords: Diabetes mellitus; awareness; obesity

Amaç: Diabetes mellitus (DM) ve obezite (OB), diğer ülkelerde olduğu gibi Türkiye’de de giderekbüyüyen problemlerdir. Fakat halkın bu sorunların karşışındaki farkındalığı sorunların önlenmesi için yeteri değildir. Bu çalışmada, bizde sokaktaki insanın DM ve OB’ının farkındalığının özel olarak tasarrufunun bir anketle değerlendirilmesi hedeflenmiştir.


Bulgular: Yapılan anketlerin sonuçlarına göre sadece %30.1 gönüllü DM ve OB farkındalığına sahipti. Diyabet ve OB bilgi düzeyi ile cinsiyet arasında anlamlı bir istatistiksel ilişki saptanamadı (p=0.05). Üniversite eğitimi alan gönüllüler en yüksek bilgi düzeyine sahipti. En az bilgi düzeyine sahip olanlar ise sosyoekonomik düzeyi düşük gönüllülerdi. Fakat artışta olanlar, sosyoekonomik düzeyi yüksek/çoğunluklu olmak ve bilgi düzeyi beklenliği gibi yüksek olmadığı değerlendirildi.

Tartışma: Elde ettiği sonuçlar DM ve OB farkındalığının orta düzeyde olduğuna işaret etse de sonuçlar ülkemizde sırasıyla 6,5 ve 15,2 milyon insana etkileyen bu sorunların yeteri değildir. Fakat gençler arasında farkındalığın yüksek olduğu olduğunu görmek umut verici olarak nitelendirebilir.

Anahtar kelimeler: Diabetes mellitus; farkındalık; obezite

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Introduction

The prevalence of diabetes mellitus (DM) is on the rise in the developed and developing countries due to changes in lifestyle (1). Type 2 DM is the most frequent type of diabetes (2). There were 135 million patients with type 2 DM in 1995 and this number is expected to rise to around 438 million by 2025 (3,4). Similarly to other countries around the world, the prevalence of DM is increasing tremendously in Turkey. A cross-sectional survey, the Turkish Epidemiology Survey of Diabetes, Hypertension, Obesity, and Endocrine Diseases (TURDEP-1) conducted between 1997 and 1998, comprised a national representative sample of 24,788 Turkish adults (aged ≥ 20 years). The same survey known as TURDEP-2 was conducted (n = 26,499) at the same centers in 2010, 12 years after the first one. The prevalence of type 2 DM was 7.2% in 1998 according to results of TURDEP-1 that increased to 13.7% (an increase of 90% in 12 years according to results of TURDEP-2). According to this study, the prevalence of impaired glucose tolerance (IGT), obesity, and central obesity was elevated to 106, 40, and 35%, respectively (5). In addition, age, hypertension, waist measurement, body mass index (BMI), low level of education, and living environment in women and age, BMI, and hypertension in men were found to be independently associated with an increased prevalence of DM.

DM reduces the life expectancy by about 5–10 years (6). It ranks fifth on the list of mortality rates of various diseases (7,8). The risk of cardiovascular diseases is two to four times higher in diabetic adults (9). Moreover, DM has been found to be the most frequent reason for renal replacement therapy or blindness among population less than 65 years. It is also associated with the amputation without trauma. Furthermore, the cost of these complications is very high (6). The cost involved in the treatment of DM constitutes 3% to 12% of the total health care expenditure in some countries (10).

The main reasons for the growing number of DM cases can be listed as the increasing population, aging, problems due to urbanization, and the reduced physical activity (11). In fact, the majority of the risk factors associated with DM can be avoided (12). Some studies suggest that the risk of DM can be reduced only by a change in an individual’s lifestyle (13,14). We believe that increasing the awareness about DM can act as a pivotal factor for its prevention in the long run. In the present study, our goal was to evaluate the level of awareness about DM and OB, as the prevalence of DM is rapidly increasing in Turkey and is intricately associated with OB.

Material and Methods

<table>
<thead>
<tr>
<th><strong>Test Your Knowledge About Diabetes</strong></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>The development of diabetes depends on excessive consumption of sweet foods</td>
<td>Yes</td>
<td>No</td>
<td>Don't Know</td>
</tr>
<tr>
<td>Is it possible to prevent diabetes</td>
<td>Yes</td>
<td>No</td>
<td>Don't Know</td>
</tr>
<tr>
<td>Diabetes symptoms always appear</td>
<td>Yes</td>
<td>No</td>
<td>Don't Know</td>
</tr>
<tr>
<td>Less physical activity is one of the causes of diabetes</td>
<td>Yes</td>
<td>No</td>
<td>Don't Know</td>
</tr>
<tr>
<td>Advanced age is a risk factor for diabetes</td>
<td>Yes</td>
<td>No</td>
<td>Don't Know</td>
</tr>
<tr>
<td>Type 2 diabetes occurs only in adults and elderly people</td>
<td>Yes</td>
<td>No</td>
<td>Don't Know</td>
</tr>
<tr>
<td>Is there a relationship between impaired glucose tolerance (prediabetes) and diabetes</td>
<td>Yes</td>
<td>No</td>
<td>Don't Know</td>
</tr>
<tr>
<td>Insulin is the only treatment for diabetes</td>
<td>Yes</td>
<td>No</td>
<td>Don't Know</td>
</tr>
<tr>
<td>Some patients with type 2 diabetes may need insulin</td>
<td>Yes</td>
<td>No</td>
<td>Don't Know</td>
</tr>
<tr>
<td>Small changes in weight, for example, slight weight loss can affect diabetes positively</td>
<td>Yes</td>
<td>No</td>
<td>Don't Know</td>
</tr>
</tbody>
</table>

Did you know the diet and physical activity can affect diabetes?

- Daily exercise less than 30 minutes may benefit health: Yes | No | Don't Know
- Can exercise reduce the blood glucose levels? Yes | No | Don't Know
- Diet plus exercise may help to normalize the blood glucose level? Yes | No | Don't Know
- The first step to weight loss is reducing the number of meals by skipping the meals? Yes | No | Don't Know
- Should elderly patients (age 65 and over) with diabetes exercise? Yes | No | Don't Know
- Exercise reduces the requirement of the medications? Yes | No | Don't Know
- Low-calorie foods can be freely consumed? Yes | No | Don't Know
- Diabetic patients can consume freely sugarless desserts? Yes | No | Don't Know
- Diabetic patients can drink alcohol? Yes | No | Don't Know
- The best way to weight loss is consuming foods rich in proteins and low carbohydrates? Yes | No | Don't Know
- Should patients with diabetes measure the blood glucose levels before the exercise? Yes | No | Don't Know
- The patients who used to have insulin have to consume the high-carbohydrate food more than others. Yes | No | Don't Know
- Consuming fruit juice a better choice than fruit itself? Yes | No | Don't Know
- Patients with type 1 diabetes have to exercise if their blood glucose is very high? Yes | No | Don't Know
- Should patients with renal impairment exercise? Yes | No | Don't Know

The questionnaire, which was proposed by the International Diabetes Federation (IDF) to evaluate the knowledge of how diet and physical activity affect DM and OB among Turkish people was validated according to the lifestyle of Turkey. The original Turkish questionnaire translated into English is given below.
The present study was a population-based cross-sectional study. After we obtained the approval of the Local Ethics Committee, the procedure was carried out on 1,000 participants in different areas of Istanbul. The sample age was between 18 and 75 years. The malls and the underground stations were listed in alphabetic order. We used cluster random sampling with random sequence generator at www.random.org, and the first 10 places were selected to ask people to fill out the questionnaires between January and June 2014. The application of the questionnaires was prepared by medical students who were trained about the questionnaire, and the volunteers willing to participate answered the questions. This questionnaire consisted of 25 questions and each correct answer was scored as 1 point. The participants were classified according to their scores that helped to categorize them based on their knowledge of DM. We determined the group having scores between 25 and 16 as high awareness (HA), the ones with scores between 15 and 11 as awareness (A), and the ones with scores less than or equal to 10 as unawareness (UA, Figure 1).

The level of knowledge of the participants about DM and OB was evaluated. Also, the age, gender, socioeconomic status (SES), the level of education, and having DM or a family history of DM were noted, and further investigations on the relationship between the level of knowledge about DM and OB and other factors was realized.

### Statistical Analysis

The statistical analyses were performed using the Social Sciences® for Windows® (version 21, SPSS, Chicago, IL, USA) software. Student’s t-test, Mann–Whitney U test, Kruskal–Wallis test, and one-way analysis of variance (ANOVA) were used to detect the specific contribution of each variable to the knowledge of awareness. Univariate and multivariate logistic regression models were built to evaluate the factors predicting awareness.

### Results

A total of 1,000 participants (537 women [53.7%] and 463 men [46.3%]) with the mean age 38.4 ±15.14 years (range 18–75 years) were included in the study. Unfortunately, there was no participant having a score between 16 and 25. Only 30.1% of the participants scored 11–15 points and were aware of the problem; the rest of the participants constituting 69.9% of the total scored less than or equal to 10 points on the questionnaire and constituted the unaware category. The general characteristics of the participants and mean scores of groups are presented in Tables 1 and 2, respectively.
When we compared the results by the means of gender, the scores were similar in males and females (p = 0.590, Table 2). The mean scores of awareness about DM and OB were found to be at the highest level with 13.58 ± 3.34 points among people aged less than 20 years and were at the lowest level with 12.48 ± 3.66 points among people aged 40 to 59 years (Table 2). There was a statistical difference among all the groups (p < 0.05), but there was no statistical difference between the awareness of DM and age groups in binary comparisons (p > 0.05, Table 2).

The level of knowledge about DM and OB significantly differed when the participants were classified by SES and the level of education (p = 0.025 and < 0.001, respectively, Table 2). Mean scores of knowledge about DM and OB were found to be in the lowest level among people with low SES; however, even people with high/very high SES had lower mean scores of awareness than the moderate SES group (Table 2). As indicated in Table 2, the participants with a history of diabetes in their families had significantly higher scores than the others (p < 0.001). Awareness was higher among the people with DM with a mean score of 14.94 ± 3.59 in the diabetic group (p < 0.001, Table 2).

We investigated the existence of any relationship between the knowledge level about DM and OB and other factors such as age, gender, SES, formal education, having DM, and a family history of DM. The results were analyzed with univariate ANOVA test and multiple logistic regression model (Tables 3 and 4). The statistical significances were based on SES, education, DM, and a family history of DM according to the univariate analysis. In the multivariate analysis based on these data, the significance was determined by education, DM, and a family history of DM.

### Discussion

The incidence of DM is increasing rapidly (11). The factor that adds to the problem is that half of the diabetic patients possess a limited knowledge about their illness and are not aware of the possible complications that may occur in the future. In the recent years, some organizations involved in improving the quality of life are making efforts to increase awareness about DM. People around the world, especially in the developing countries lack the sufficient knowledge of DM and OB (15,16). A lack of interest, cultural factors, lack of opportunities, and inadequate disclosure about DM by the governments are seemed to be the major reasons related to the low DM awareness. In this regard, the present study is one of the rare studies in Turkey. Pakistani and Iranian studies reported female participants to be less aware of DM than their male counterparts (16,17). However, in another Pakistani study, female participants scored higher in terms of awareness about DM when compared to males (18). Also, in a Turkish study, male diabetic patients were more likely to be informed than the female patients (15). But in our study, no gender-based differences were observed with respect to awareness on DM and OB. A possible underlying reason may be the cultural differences. Most of our participants were of Turkish origin and resided in the urban areas, which might have contributed to the indifference.

A number of studies are available in the literature that report the rural and low-income populations to be less aware of DM, whereas a higher level of education causes an increase in diabetes knowledge (17-21). A study from Cameroon demonstrated that educational level had a direct influence on the level of knowledge regarding topics such as risk factors, symptoms, complications, and the management of DM (22). The results of these studies are similar to our study. This may be attributed to the fact that uneducated people with low income who have experienced several difficulties in retrieving any kind of information throughout their lives due to lack of facilities, were not aware of DM and OB as expected.

In our study, we demonstrated that the participants with an age less than 20 years had the highest scores of knowledge on DM, whereas the participants with age between 40 and 59 years had the lowest scores of diabetic awareness. According to a study on investigating the awareness of diabetes, no significant differences were observed among the scores of participants be-

### Table 3. The factors that were associated with awareness (Univariate)

<table>
<thead>
<tr>
<th>Age (vs. &lt;20 years)</th>
<th>B</th>
<th>p</th>
<th>OR</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-39 years</td>
<td>-0.445</td>
<td>0.015</td>
<td>0.641</td>
<td>0.447</td>
<td>0.918</td>
</tr>
<tr>
<td>40-59 years</td>
<td>-0.347</td>
<td>0.094</td>
<td>0.707</td>
<td>0.471</td>
<td>1.061</td>
</tr>
<tr>
<td>&gt;60 years</td>
<td>0.093</td>
<td>0.731</td>
<td>1.098</td>
<td>0.644</td>
<td>1.872</td>
</tr>
<tr>
<td>Gender</td>
<td>-0.012</td>
<td>0.953</td>
<td>0.988</td>
<td>0.659</td>
<td>1.483</td>
</tr>
</tbody>
</table>

### Table 4. The factors that were associated with awareness (Multivariate)

<table>
<thead>
<tr>
<th>SES (vs. poor)</th>
<th>B</th>
<th>p</th>
<th>OR</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Middle</td>
<td>0.335</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>0.226</td>
<td>0.213</td>
<td>1.253</td>
<td>0.878</td>
<td>1.787</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Education (vs. &lt;5 years)</th>
<th>B</th>
<th>p</th>
<th>OR</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>High school</td>
<td>-0.072</td>
<td>0.658</td>
<td>0.931</td>
<td>0.677</td>
<td>1.279</td>
</tr>
<tr>
<td>University</td>
<td>0.522</td>
<td>0.001</td>
<td>1.685</td>
<td>1.242</td>
<td>2.288</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diabetes Yes (vs. No)</th>
<th>B</th>
<th>p</th>
<th>OR</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history DM (vs. No)</td>
<td>1.270</td>
<td>0.019</td>
<td>3.562</td>
<td>1.232</td>
<td>10.299</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Constant</th>
<th>B</th>
<th>p</th>
<th>OR</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.297</td>
<td>0.000</td>
<td></td>
<td></td>
<td>3.640</td>
<td></td>
</tr>
</tbody>
</table>
longing to different age groups. However, the participants aged 20 to 35 years and 36 to 50 years had the highest scores and participants aged less than 20 years; those more than 50 years of age had the lowest scores (18). Also, another study showed old age to be a major barrier toward knowledge about DM (23). Our results were similar to the above-mentioned study for the aged participants. However, the highest number was scored by young people. Surprisingly, the population above 60 years of age had greater awareness as compared to age groups of 20 to 39 and 40 to 59 years. The reason could be the inclusion of elderly population, especially, retired people who supposed to have more free time to collect all kinds of information about DM.

In one of the rare Turkish studies about awareness of DM, it was demonstrated that the total level of awareness of DM was 28.6% in 1,334 diabetic patients. Caliskan et al. showed in their multivariate analyses that patients who had university degree were 13.5 times more likely to be well-informed about DM compared to other groups (15). In our study, people with a university degree were 1.7 times more aware than the illiterate/primary group. Furthermore, people with DM were three times more aware than people without DM. It is known from the literature that if there is a family history of a disease, it could lead to higher level of awareness among other members of that family (24). The possible risk factors are the primary motivations that can change the health belief model with less risky behavior (25). Harwell et al. showed an association between the likelihood of a risk of DM and its presence in family history in their study (26). However, some studies also exist with a contradictory argument. Pierce et al. reported, in a randomized controlled study, that the individuals who had family members with type 2 DM did not care about their own health risks (27). In our study, we found that the participants with DM in their family history were 1.8 times more aware than others. The underlying reason might be their opportunity to collect wider information when the participants had other family members with DM. But another study from Turkey about DM awareness suggests that there was no relationship between the knowledge about DM and presence of health insurance, DM history in the family, comorbidities, blood pressure levels, BMI values, and smoking status (15).

In conclusion, the level of awareness about DM and OB is moderate in a Turkish population. The fact that the prevalence of DM and OB reached 2.6 and 8.5 million, respectively, the present level of knowledge is insufficient to improve the diabetic health crisis. Improving the level of awareness among the general population can help patients with DM as well as people with a history of DM in their families to take better care of the disease.

Acknowledgements

We especially thanks to Dilara Karsidag for English Editing.

Ethics

The study was accepted by Local Ethics Committee of Istanbul Medical Faculty. Participants’ informed consent form was filled out with the help of students.

Author Contributions


Conflict of Interest: The authors declare that they have no conflict of interest.

Financial Disclosure: There is no organization that funded our research.

References


Subclinical Hypothyroidism is Associated with Atherogenic Lipid Profile in Postmenopausal Women

Subklinik Hipotiroidizm Menopoz Sonrasinda Aterojenik Lipid Profiliyle İlişkilidir


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Abstract

Purpose: To determine the prevalence and association of atherogenic lipid profile in postmenopausal women with subclinical hypothyroidism.

Materials (Subjects) and Methods: This was a prospective clinical study included 140 postmenopausal women. In all subjects, basic sociodemographic and anthropometric data, hormonal status of the thyroid gland, and lipid profile were determined. The subjects were followed for a period of 30 months.

Results: The subclinical hypothyroidism in postmenopausal women was significantly associated with higher levels of serum cholesterol, triglycerides, LDL-C, and lower HDL-C (p=0.009, p=0.01, p=0.023, p=0.001, respectively). Furthermore, the analysis of repeated measures showed that subclinical hypothyroidism, irrespective of age and duration of postmenopause, was associated with higher levels of serum cholesterol (adjusted beta: 0.43, CI: 0.12, 0.74, p=0.007), triglycerides (adjusted beta: 0.52, CI: 0.21, 0.84, p=0.001) and LDL-C (adjusted beta: 0.35, CI: 0.03, 0.67, p=0.03), and lower levels of serum HDL-C (adjusted beta: -0.48, CI: -0.81, 0.15, p=0.004).

Conclusion: Subclinical hypothyroidism is associated with atherogenic lipid profile in postmenopausal women.

Keywords: Subclinical hypothyroidism; atherogenic lipid profile; postmenopause

Özet

Amaç: Subklinik hipotiroidizm olan postmenopozal kadınlarda aterojenik lipid profilinin prevalansını ve ilişkisini belirlemektir.

Gereç (Olgular) ve Yöntemler: Prospektif klinik çalışma 140 postmenopozal kadın içermiştir. Tüm olgulara temel sosyodemografik ve antropometrik verileri, tiroid bezinin hormonal durumu ve lipid profilini belirlemiştir. Olgular 30 ay süreyle takip edilmiştir.

Bulgular: Postmenopozal kadınlarda subklinik hipotiroidizm daha yüksek serum kolesterol, trigliserid, LDL-C düzeyleri ve daha düşük HDL-C düzeylerileyle anlamlı düzeyde ilişkilidir (sırasyla, p=0,009, p=0,01, p=0,023, p=0,001). Dahasi, tekrarlanan ölçümlerin analizleri subklinik hipotiroidizmin, yaş ve menopoz süresinden bağımsız olarak; daha yüksek serum kolesterol (uyarlanmış beta: 0,43, CI: 0,12, 0,74, p=0,007), trigliserid (uyarlanmış beta: 0,52, CI: 0,21, 0,84, p=0,001) ve LDL-C (uyarlanmış beta: 0,35, CI: 0,03, 0,67, p=0,03) ve daha düşük serum HDL-C (uyarlanmış beta: -0,48, CI: -0,81, 0,15, p=0,004) düzeylerileyle ilişkili olduğunu göstermiştir.

Sonuç: Subklinik hipotiroidizm postmenopozal kadınlarda aterojenik lipid profiline ilişkilidir.

Anahtar kelimeler: Subklinik hipotiroidizm; aterojenik lipid profil; postmenopozal

Introduction

Subclinical hypothyroidism (SH) is defined as an elevated serum level of thyroid stimulating hormone (TSH) with the normal levels of free thyroxine (FT4) and free triiodothyronine (FT3) (1). Most patients are symptomless and have serum TSH levels <10 mU/L. In the studies conducted on the general population, the prevalence of subclinical hypothyroidism ranges from 4% to 15% (2).
Dyslipidemia is defined as an increase in the levels of total cholesterol, low-density lipoprotein cholesterol (LDL-C) and triglycerides (7). The patients with dyslipidemia have an increased risk of atherosclerosis, which might lead to cardiovascular disease—reported as the main cause of death in a younger age (8).

Menopause is defined as having occurred when a woman has not had any vaginal bleeding for more than one year due to a decrease in ovarian hormone production. Menopause occurs most often between 49 and 52 years of age (9). Postmenopausal phase has a high risk of cardiovascular diseases that indicates progression of ageing. Postmenopausal women, as compared to premenopausal women, have a higher prevalence of metabolic syndrome (10). Waist circumference, waist-to-hip ratio, blood pressure and the levels of fasting glucose are higher in postmenopausal women compared to women before menopause (11). Compared to premenopausal women, postmenopausal women have higher total serum cholesterol and LDL-C levels (12).

It has already been established that estrogens have a profound effect on the endothelium and smooth muscle cells in the vascular wall, thereby causing vasodilatation (13). Estrogens also exert some effect on hepatic cells by decreasing LDL-C and increasing HDL-C concentrations in blood (14). A decrease in the level of estrogens is related to an increase in fatty tissue in postmenopausal women (15). The decrease in estrogen results in atherogenic lipid profile in postmenopausal women (16,17). The process of subclinical atherosclerosis can be well controlled and even reversed if diagnosed on time and treated by improving hormonal and metabolic control.

Recent studies suggest that subclinical hypothyroidism can be a potentially modifiable risk factor for cardiovascular disease. Since subclinical hypothyroidism is more prevalent in older women than in any other population group (3), it is important to investigate the association between SH and lipid profile in postmenopausal women.

Objective

The aim of this study was to determine the prevalence and association of atherogenic lipid profile in postmenopausal women with subclinical hypothyroidism.

Materials and Methods

Study design and data collection

This prospective case-controlled clinical study included 140 postmenopausal women at the clinic for endocrinology, diabetes and metabolic diseases, Clinical Center of Sarajevo University. Sixty-one postmenopausal women with SH were compared with 79 age and BMI-matched euthyroid controls. Menopause was considered when a woman did not have vaginal bleeding for more than one year. SH was defined as TSH greater than 4.2 mU/L with normal FT4 and FT3. Dyslipidemia was defined as serum levels of LDL-C >4.30 mmol/L, total cholesterol >5.20 mmol/L, triglycerides >1.70 mmol/L, and HDL-C <1.06 mmol/L. A smoker was defined as a person who smokes tobacco regularly. Physical activity was defined as any movement of the body that requires energy expenditure (walking, gardening, climbing the stairs, running, other forms of physical exercise) for at least 30 min on a daily basis. Exclusion criteria were renal failure, hepatic failure, diagnosed or already treated hypothyroidism. After signing an informed consent, all postmenopausal women in the study were subject to a thorough physical examination and the following data were collected: age, duration of postmenopause, basic lifestyle factors (smoking habits, physical activity), thyroid gland (TSH, FT3, FT4), lipid profile (cholesterol, triglycerides, HDL-C, LDL-C). The parameters of the thyroid gland (hormonal status) and lipid metabolism were determined by ELISA (Cobas e411 and Cobas 6000 Biochemistry Analyzer Roche Diagnostics GmbH, Japan, 2009). The study was conducted in accordance with the World medical association Declaration of Helsinki on ethical principles for medical research involving human subjects (2008, Revised), and was approved by the Ethics Committee of the Clinical Center of Sarajevo University.

Statistical analysis

The data for continuous variables were presented as means, median, and standard deviation, and for categorical variables as absolute and relative frequencies. In order to determine the difference of means between the two groups, continuous variables were compared using either t-test (normal distribution) or the Mann-Whitney test (non-normal distribution). The role of subclinical hypothyroidism was examined using the multivariate logistic regression analysis. The odds ratio was calculated with the corresponding index of confidentiality. Wherever the sample permitted, an appropriate modeling was done for the evaluation of predictors in relation to the dependent variable logistic regression analysis. A statistical significance was interpreted as p ≤ 0.05. The data were presented in the form of tables and figures. SAS (Statistical Analysis system) software Version 9 for Microsoft Windows (SAS Institute Inc., Cary, NC, USA) was used for data processing and all statistical analyses.

Results

The study included 140 postmenopausal women (61 with confirmed subclinical hypothyroidism and 79 euthyroid controls). Table 1 presents reference values of laboratory tests used in the study. The mean value of TSH in the women with subclinical hypothyroidism was significantly higher compared to the mean value of TSH in the euthyroid women (6.4 ±1.2 mU/L vs. 2.4 ±1.1 mU/L; P = 0.0001). The period of postmenopause in women with subclinical hypothyroidism was longer but the difference was not statistically significant compared to euthyroid women (7.0 ±3.3 vs. 6.1 ±3.5 years; P = 0.099). The number of non-smokers was higher in both groups compared to smokers. In the group with subclinical hypothyroidism, 91.8% of the women were non-smokers, while in the euthyroid group 78.5% of the women were non-smokers (P = 0.032).
There was a statistically significant difference between the groups regarding their physical activity, with 91.8% of the women with subclinical hypothyroidism being physically active, compared to 74.7% of the euthyroid women (P = 0.009).

The mean values of serum cholesterol were significantly higher in postmenopausal women with subclinical hypothyroidism compared to the euthyroid postmenopausal women (6.12 ±0.91 mmol/L vs. 5.68 ±1.02 mmol/L; P=0.009). The mean values of serum triglycerides were significantly higher in postmenopausal women with subclinical hypothyroidism compared to euthyroid postmenopausal women (1.90 ±0.49 mmol/L vs. 1.57 ±0.58 mmol/L; P=0.01).

The mean values of serum HDL-C were significantly lower in postmenopausal women with subclinical hypothyroidism compared to euthyroid postmenopausal women (1.20 [1.03 – 1.38] mmol/L vs. 1.41 [1.21 – 1.63] mmol/L; P=0.001). The mean values of serum LDL-C were significantly higher in postmenopausal women with subclinical hypothyroidism compared to euthyroid postmenopausal women (4.20 [3.67 – 4.65] mmol/L vs. 3.91 [3.19 – 4.34] mmol/L; P=0.023).

The postmenopausal women were followed for a period of 30 months. The laboratory parameters of lipid status were determined at the beginning and at 6th, 18th, and 30th months. Follow-up measurements are shown in Table 2.

The analysis of repeated measures showed that subclinical hypothyroidism, independent of age and duration of postmenopause, is associated with higher levels of serum cholesterol (adjusted beta: 0.43, CI: 0.12, 0.74, p=0.007), triglycerides (adjusted beta: 0.52 ,CI: 0.21, 0.84, p=0.001) and LDL-C (adjusted beta: 0.35 ,CI: 0.03, 0.67, p=0.03), and lower levels of serum HDL-C (adjusted beta: –0.48 ,CI: –0.81, 0.15, p=0.004), as shown in Figure 1.

Discussion

Several studies have shown that the morbidity due to cardiovascular disease is approximately six times lower in women of reproductive age compared to the men in the matched age groups (18).

There was a statistically significant difference between the groups regarding their physical activity, with 91.8% of the women with subclinical hypothyroidism being physically active, compared to 74.7% of the euthyroid women (P = 0.009). The mean values of serum cholesterol were significantly higher in postmenopausal women with subclinical hypothyroidism compared to the euthyroid postmenopausal women (6.12 ±0.91 mmol/L vs. 5.68 ±1.02 mmol/L; P=0.009). The mean values of serum triglycerides were significantly higher in postmenopausal women with subclinical hypothyroidism compared to euthyroid postmenopausal women (1.90 ±0.49 mmol/L vs. 1.57 ±0.58 mmol/L; P=0.01).

The mean values of serum HDL-C were significantly lower in postmenopausal women with subclinical hypothyroidism compared to euthyroid postmenopausal women (1.20 [1.03 – 1.38] mmol/L vs. 1.41 [1.21 – 1.63] mmol/L; P=0.001). The mean values of serum LDL-C were significantly higher in postmenopausal women with subclinical hypothyroidism compared to euthyroid postmenopausal women (4.20 [3.67 – 4.65] mmol/L vs. 3.91 [3.19 – 4.34] mmol/L; P=0.023).

The postmenopausal women were followed for a period of 30 months. The laboratory parameters of lipid status were determined at the beginning and at 6th, 18th, and 30th months. Follow-up measurements are shown in Table 2.

The analysis of repeated measures showed that subclinical hypothyroidism, independent of age and duration of postmenopause, is associated with higher levels of serum cholesterol (adjusted beta: 0.43, CI: 0.12, 0.74, p=0.007), triglycerides (adjusted beta: 0.52 ,CI: 0.21, 0.84, p=0.001) and LDL-C (adjusted beta: 0.35 ,CI: 0.03, 0.67, p=0.03), and lower levels of serum HDL-C (adjusted beta: –0.48 ,CI: –0.81, 0.15, p=0.004), as shown in Figure 1.

Discussion

Several studies have shown that the morbidity due to cardiovascular disease is approximately six times lower in women of reproductive age compared to the men in the matched age groups (18).
The incidence of cardiovascular diseases in women increases after 50 years of age (19). This increased risk can be attributed to a decline in the estrogen levels after the menopausal transition (20). The studies carried out in postmenopausal women have reported an inverse relation between estrogen levels, dyslipidemia, and atherosclerosis (21,22). The improvements in lipid profile following hormonal replacement therapy have been established in postmenopausal women (23).

Lipid status was evaluated among the subjects. The mean values of serum total cholesterol, triglycerides, and LDL-C in postmenopausal women with subclinical hypothyroidism at the baseline were significantly higher than the mean values of serum cholesterol, triglycerides, and LDL-C of euthyroid postmenopausal women. The mean value of serum HDL-C in women with subclinical hypothyroidism at the baseline was significantly lower than the mean serum value of HDL-C in euthyroid postmenopausal women. Furthermore, our analysis of repeated measures showed that subclinical hypothyroidism independent of age and duration of postmenopause is associated with an increase in serum total cholesterol, triglyceride and LDL-C values, and a decrease in HDL-C values.

The cross-sectional study of Meuwese et al. showed that patients with mildly elevated TSH (between 5.1 and 10.0 mU/L) had significantly higher levels of cholesterol than those who were euthyroid (3). Posadas-Romero et al. (24) found that patients with subclinical hypothyroidism have significantly higher triglyceride levels and decreased HDL-C.

Similar results were observed by Siemiński et al. (25), who found elevated serum concentrations of cholesterol and triglycerides, while HDL-C was lower in women with subclinical hypothyroidism compared to the euthyroid postmenopausal women. Heima et al. (26) also established the association between dyslipidemia and subclinical hypothyroidism.

The exact pathophysiological mechanism accounting for the effects of TSH on lipid profile has not been fully established. Tian et al. (27) proposed that TSH upregulates the expression of hepatic 3-hydroxy-3-methyl-glutaryl coenzyme A reductase (an enzyme that limits cholesterol synthesis) by acting on the TSH receptor on liver cells. Gagnon et al. (28) showed that TSH stimulates lipolysis in cultured adipocytes and elevates serum-free fatty acid levels.

The elevated TSH levels in the serum of patients with SH suggest that, although apparently normal, serum thyroid hormones are insufficient. Thyroid hormone deficiency, therefore, represents a well-known cause of dyslipidemia, both in overt and subclinical hypothyroidism (29).

Our study has several limitations such as a small sample size and the relatively short follow-up time. The inconsistencies between our and previous studies may be explained by the differences in the study design, sample size, population characteristics, as well as the criteria used to define the dysfunction of the thyroid gland. Larger cohort studies with a longer duration in our population are required in order to evaluate the further consequences of subclinical hypothyroidism as the mildest form of thyroid gland dysfunction. This study has several advantages, including a longitudinal design and implication of repeated measures. Also, we were able to control our analysis for the age and duration of postmenopause. Additionally, all measurements were valid and the data were collected using the recommended modern equipment. To the best of our knowledge, this is the first study with multiple measurements related to the subclinical hypothyroidism and its consequences carried out on Bosnia and Herzegovina population.

Conclusion
Subclinical hypothyroidism is significantly associated with higher levels of serum total cholesterol, triglycerides, LDL-C, and lower HDL-C. Our analysis of repeated measures during the 30-months follow-up showed that subclinical hypothyroidism independent of the age and duration of postmenopause is associated with higher levels of serum cholesterol triglycerides, LDL-C, and lower HDL-C. Our study confirms that elevated serum TSH in patients with subclinical hypothyroidism is associated with atherogenic lipid profile and increases the risk of developing cardiovascular diseases, regardless of other known risk factors.

Ethics
Research was approved by the Ethics Committee of Clinical Center University of Sarajevo.

Authorship Contributions

Conflict of Interest: No conflict of interest was declared by the authors.

References
Aetiology of Spontaneous Hypoglycaemia in a South African Hospital

Bir Güney Afrika Hastanesinde Spontan Hipoglisleminin Etiyolojisi

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Abstract

Purpose: To determine the etiology of spontaneous hypoglycaemia at admissions in Nelson Mandela Central Hospital, Mthatha, Eastern Cape, South Africa.

Material and Method: A retrospective review of medical records for the patients admitted with spontaneous hypoglycaemia from January 2008 till December 2015 was carried out. The medical records of patients with blood glucose levels <2.5 mmol/L were reviewed for age, gender, relevant medications, alcohol history, retroviral status, blood glucose, plasma insulin, C-peptide, ketone, cortisol, IGF-1 level, liver and kidney function, and documented etiology of hypoglycaemia.

Results: There were 26 patients (65.4% females) with the mean age of 39.6±22.3 years (range 13–95 years). The mean blood glucose levels during hypoglycemic episodes were 1.6±0.6 mmol/L (range 0.5–2.9 mmol/L). Half of the patients (n=13/26) were retroviral positive. Hypoglycaemia was associated with the elevated or inappropriately normal plasma insulin levels in 35.3% subjects and with the suppressed plasma insulin levels in 64.7% of cases. Eight cases of spontaneous hypoglycaemia were pregnancy related. All pregnancy related cases of hypoglycaemia were noted in retroviral positive subjects. The main cause for hypoglycaemia was hypocortisolism.

Discussion: The admissions in the case of spontaneous hypoglycaemia were mainly due to hypocortisolism. All pregnant and postpartum patients with spontaneous hypoglycaemia were retroviral positive.

Keywords: Hypoglycaemia; hypocortisolism; retroviral disease; pregnancy

Özet

Amaç: Nelson Mandela Merkez Hastanesi, Mthatha, Doğu Cape, Güney Afrika, spontan hipoglislemini müracaatlarının etiyolojisini belirlemektedir.


Bulgular: Toplam 26 hastanın (%65,4 kadın) ortalama yaş 39,6±22,3 yıl ve yaş aralığı 13 ile 95 arasındadır. Ortalama kan glukoz düzeyleri hipoglislemini atakları esnasında 1,6±0,6 mmol/L ve 0,5–2,9 mmol/L aralığındadır. Hastaların yarısı (n=13/26) retroviral pozitiftir. Hipoglisleminin, hastaların %35,3’ünde yükselmüş veya uygun olmayan normal plazma insülin düzeyleriyle ve %64,7’sinde baskılanmış plazma insülin düzeyleriyle ilişkilidir. Sekiz spontan hipoglislemini olgusu gebelikle ilişkilidir. Tüm gebelikle ilişkili hipoglislemini olguları retroviral pozitif hastalardardır. Hipoglisleminin esas nedeni hipokortizolizmdir.

İşçihan: Spontan hipoglislemini müracaat esas olarak hipokortizolizme bağlıdır. Hipoglislemini tüm gebe ve postpartum hastalar retroviral pozitiftir.

Anahtar kelimeler: Hipoglislemin; hipokortizolizm; retroviral hastalık; gebelik
Introduction

Spontaneous hypoglycaemia is a term used for low blood glucose unrelated to therapy for diabetes. Hypoglycaemia is classically diagnosed based on the Whipple's triad of documented low blood glucose level, symptoms and signs of hypoglycaemia with relief after normalization of blood glucose (1). Diabetes related treatment is the commonest reason for hypoglycaemia admissions (2-4). Diabetes related hypoglycaemia is usually due to the use of medications that raise plasma insulin levels and is more common with Type 1 than Type 2 diabetes (5,6). Spontaneous hypoglycaemia, not related to diabetes may be categorized as fasting or post-prandial. Reported causes of fasting hypoglycaemia include endogenous hyperinsulinaemic states such as insulinoma, insulin antibody and insulin receptor antibody (7-10). Non-hyperinsulinaemic associated causes of hypoglycaemia include septicaemia, alcohol ingestion, renal failure, liver failure and malignancies secreting IGF-2 (11-14). A rare but familial cause of hypoglycaemia is Type B insulin resistance which is due to the binding of antibodies to the insulin receptor (15). Post prandial hypoglycaemia typically occurs within 1-3 hours of meal ingestion as a result of rapid intestinal transport of glucose (16). Drug induced causes of hypoglycaemia include deliberate or accidental administration of insulin or insulin secretagogues such as sulphonylureas and meglitinides, quinolones such as gatifloxacin and clinafloxacin, quinine, pentamidine, betablockers, angiotensin converting enzyme inhibitors and venlafaxine (17-20). The mechanisms of drug induced hypoglycaemia range from increased stimulation of insulin secretion, decreased clearance of insulin and interference of glucose metabolism (17). Endocrinopathies that can cause or contribute to hypoglycaemia include hypoadrenalism, growth hormone deficiency and hypothyroidism (21-23).

While hypoglycaemia can be immediately corrected by administering glucose to the patient, definitive therapy can only be ensured by ascertaining the underlying aetiology.

There is no published report on the aetiology of patients who present with spontaneous hypoglycaemic episodes in our environment. This study aims to report the aetiology of patients who present with spontaneous hypoglycaemia in our hospital.

Methods: This is a retrospective review of hospital records over the 7-year period from January 2008 till December 2015. Subjects are all adult patients admitted into Nelson Mandela Academic hospital for non-diabetes related hypoglycaemia from 2008 to 2015 for whom records are available. Patients' medical records were reviewed for age, gender, relevant drugs and alcohol history, retroviral status, laboratory parameters (blood glucose, liver function, kidney function, plasma insulin, C-peptide, ketone, cortisol, IGF-1 level and documented cause of hypoglycaemia).

Ethical considerations: Ethical approval for the study was obtained from the Ethics committee, Faculty of Health Sciences, Walter Sisulu University, Mthatha.

Routine Practice: Patients presenting with spontaneous hypoglycaemia are admitted for evaluation. Where the glucometer capillary blood glucose is ≤ 3 mmol/L, venous blood is taken for laboratory glucose, insulin, C-peptide, ketone, cortisol, IGF-1, liver and renal function. Correction of hypoglycaemia with a 20mL bolus of 50% glucose is then effected. Where hypoglycaemia had been corrected at the referring hospital or in our emergency ward before taking bloods that will enable the ascertainment of aetiology, the patient is fasted while on admission for a maximum of 48 hours. Fasting involves depriving the patient of all calories including oral feeds and glucose containing intravenous fluids. Patient is however allowed water orally or non-glucose containing intravenous fluids like normal saline. Patient is questioned and examined hourly for symptoms and signs of hypoglycaemia with glucometer testing for glucose obtained by a finger prick. This is continued until the glucometer glucose is ≤ 3 mmol/L when venous blood is drawn for laboratory blood glucose, liver function, kidney function, plasma insulin, C-peptide, ketone, cortisol and IGF-1 level.

Fasting is stopped before 48 hours once venous plasma samples have been collected following a glucometer reading of ≤ 3 mmol/L or at 48 hours where the glucometer reading remains persistently above 3 mmol/L. Patients presenting with alcohol induced hypoglycaemia who were treated in the emergency department and discharged home without admission into the medical wards were excluded.

The 26 patients herein reported on comprise of 19 patients that were referred from other hospitals and admitted via the medical emergency department of Nelson Mandela Central Hospital Mthatha and 8 patients admitted in the Obstetrics department of Nelson Mandela Central Hospital (5 during labour and 3 in the post-partum period).

Interpretation of Results: Hypoglycaemia is confirmed by a laboratory blood glucose < 2.5 mmol/L. Hyperinsulinaemia and elevated plasma C-peptide are respectively defined as plasma insulin ≥ 2 mIU/L and plasma C-Peptide ≥ 1 mcg/L in response to plasma glucose < 2.5 mmol/L. Hypocortisolism is defined as plasma cortisol < 500 nmol/L in response to plasma glucose < 2.5 mmol/L. Insulinoma was diagnosed based on non-suppressed plasma insulin and C-peptide of ≥ 2 mIU/L and 1 mcg/L respectively in the presence of adequate hypoglycaemia of < 2.5 mmol/L in additional to radiologic evidence of pancreatic tumour.

Hypoglycaemia is initially categorized as hyperinsulinaemic or non-hyperinsulinaemic. Hyperinsulinaemic causes include insulinoma, insulin antibodies, insulin receptor antibodies, accidental or surreptitious administration of insulin, sulfonlureas, quinine etc. Non-hyperinsulinaemic causes include alcohol ingestion, hypocortisolism, renal failure, hepatic failure and tumors that produce IGF2.

Data processing and analysis

Data was entered into an excel spread sheet and analyzed using SPSS version 21, Chicago Illinois. Continuous variables are expressed as mean ± standard deviation while categorical variables are expressed as percentages or proportions. Means of continuous variables were compared using the student’s t test while categorical variables were assessed with Chi square test. Statistical significance was taken as P ≤ 0.05.
Results
Complete results for plasma insulin, C-peptide and cortisol levels were available for 17 patients. Three patients had results for plasma C-peptide and cortisol levels but not plasma insulin levels. These 3 patients were a 59-year-old female, retroviral negative with plasma C-peptide of 0.1 mcg/L and plasma cortisol of 892 nmol/L. A second patient was a 57-year-old female, retroviral negative with plasma C-peptide of 1.8 mcg/L and plasma cortisol of 964 nmol/L while the 3rd patient was a 55-year-old male with plasma C-peptide of 1.3 mcg/L and plasma cortisol of 1464 nmol/L. This latter patient had renal failure manifested by serum creatinine of 811 mmol/L.

Six patients had no documented results for insulin, C-peptide and cortisol. They comprised of 3 males and 2 females with an age range of 13-62 years. One of these patients is a 29-year-old female on anti-retrovirals with hypoglycaemia of 1.9 mmol/L and in labour at the 24th week of gestation.

The mean age of the 26 patients is 39.6±22.3 years with an age range of 13 to 95 years. Females represented 65.4% (n=17/26) of all patients. The mean blood glucose level during the hypoglycaemic episodes was 1.6±0.6 mmol/L (0.5-2.9). Half of the patients (n=13/26) were retroviral positive. Hypoglycaemia was associated with elevated or inappropriately normal plasma insulin levels in 35.3% and suppressed plasma insulin levels in 64.7% of cases. Eight cases of spontaneous hypoglycaemia were pregnancy related (5 occurred during labour, while 3 happened post-delivery).

Table 1 shows the profiles of hyperinsulinaemic patients (n=6). All except one patient were female. Three of the patients were retroviral positive, two of whom were on anti-retrovirals. These two patients on anti-retrovirals experienced hypoglycaemic episodes post-delivery. All hyperinsulinaemic patients had elevated plasma levels of C-peptide except one patient with low plasma C-peptide of 0.3 despite raised plasma insulin of 2.1 miu/L. Three of the hyperinsulinaemic patients had optimal serum cortisol levels during the hypoglycaemic episode. In one of these patients, computerized tomogram scan revealed malrotation of the gut and in another patient, insulinoma was diagnosed following computerized tomogram scan of the abdomen and biopsy of metastatic nodules to the liver which was histologically confirmed as insulinoma.

Table 2 shows the profiles of eleven non-hyperinsulinaemic patients, comprising of eight females and three males. The majority,

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age in years</th>
<th>BG mmol/L</th>
<th>RVD status</th>
<th>Cyesis</th>
<th>Plasma Insulin miu/L</th>
<th>Plasma C-peptide mcg/L</th>
<th>Plasma Cortisol nmol/L</th>
<th>Diagnosis</th>
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</thead>
<tbody>
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<td>Neg</td>
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<tr>
<td>2</td>
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<td>39</td>
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<td>Pos on ARV</td>
<td>Post del</td>
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<td>0.3</td>
<td>332</td>
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<tr>
<td>3</td>
<td>F</td>
<td>21</td>
<td>2.1</td>
<td>Pos on ARV</td>
<td>Post del</td>
<td>7.1</td>
<td>1.4</td>
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<td>Neg</td>
<td>19.8</td>
<td>6.7</td>
<td>559</td>
<td>Malrotation of gut</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>27</td>
<td>1.6</td>
<td>Pos on ARV</td>
<td></td>
<td>4.7</td>
<td>1.1</td>
<td>762</td>
<td>Insulinoma</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>15</td>
<td>1.7</td>
<td>Neg</td>
<td>NA</td>
<td>5.3</td>
<td>2.8</td>
<td>-</td>
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</tr>
</tbody>
</table>

BG: Blood glucose, RVD: Retroviral disease, Neg: Negative, Pos: Positive, Del: Delivery, NA: Not applicable, –: Not available

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age in years</th>
<th>BG mmol/L</th>
<th>RVD status</th>
<th>Cyesis</th>
<th>Plasma Insulin miu/L</th>
<th>Plasma C-peptide mcg/L</th>
<th>Plasma Cortisol nmol/L</th>
<th>Diagnosis</th>
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</thead>
<tbody>
<tr>
<td>1</td>
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<td>&lt;0.1</td>
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<tr>
<td>3</td>
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<td>2.3</td>
<td>Neg</td>
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<td>&lt;2</td>
<td>1.9</td>
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<tr>
<td>4</td>
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<td>1</td>
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<td>8</td>
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<td>22</td>
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<td>Pos on ARV</td>
<td>31 wks</td>
<td>1.3</td>
<td>1.3</td>
<td>840</td>
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</tr>
<tr>
<td>9</td>
<td>F</td>
<td>26</td>
<td>1.6</td>
<td>Pos on ARV</td>
<td>Post del</td>
<td>1.5</td>
<td>3</td>
<td>871</td>
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</tr>
<tr>
<td>10</td>
<td>F</td>
<td>21</td>
<td>2.1</td>
<td>Neg</td>
<td>Neg</td>
<td>&lt;2</td>
<td>0.8</td>
<td>&gt;2069</td>
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<td>F</td>
<td>32</td>
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<td>Pos</td>
<td>neg</td>
<td>&lt;2</td>
<td>0.8</td>
<td>&gt;2069</td>
<td>-</td>
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</table>

(n=7/11) were retroviral positive, of which in five patients, it was pregnancy related. Nine of the eleven patients with low to suppressed plasma insulin levels also had low plasma C peptide levels. However, 2 patients had elevated plasma C peptide levels despite low plasma insulin levels. Six patients had sub-optimal plasma cortisol levels and were subsequently managed as hypoadrenalism. Five patients had optimal plasma cortisol levels despite the presence of risk factors for hypoadrenalism such as tuberculosis and cytomegalovirus infection.

Table 3 shows the profiles of all 8 pregnancy related cases of spontaneous hypoglycaemia, all of who were retroviral positive. All but one of the pregnancy related cases of hypoglycaemia were already on treatment with anti-retrovirals. In one patient, result for plasma insulin was not available, though the plasma C-peptide was elevated. Two patients were hyperinsulinaemic while 5 were non-hyperinsulinaemic. Four patients had sub-optimal plasma cortisol responses to hypoglycaemia while three patients had optimal plasma cortisol responses despite presence of risk factors for hypoadrenalism such as tuberculosis and cytomegalovirus infection. Three of these pregnancy related cases of hypoglycaemia occurred in the post-partum period of which two of these patients were acutely ill, one with puerperal sepsis and the other with disseminated tuberculosis. One patient was in a relatively stable condition.

Discussion

The majority of our patients with spontaneous hypoglycaemia were non-hyperinsulinaemic with sub-optimal plasma cortisol response that is consistent with hypocortisolism. We defined hypocortisolism as plasma cortisol < 500 nmol/L in response to hypoglycaemia of < 2.5 mmol/L. Indeed, in the majority of these patients, hypoglycaemia resolved with glucocorticoid therapy.

Three patients (patients numbered 1,2,3 in Table 1) with sub-optimal cortisol response to hypoglycaemia were however, hyperinsulinaemic. This may suggest the possibility of both hypoadrenalism and hyperinsulinaemia as operative mechanisms for hypoglycaemia in these patients. There were no records of exposure to medications that may be associated with hyperinsulinaemia. Repeated episodes of hypoglycaemia can blunt the plasma cortisol response to hypoglycaemia, but there were no documented records of previous hypoglycaemic episodes in these patients. As this is a retrospective study, it is possible that these patients may very well have a purely hyperinsulinaemic hypoglycaemia with a low cortisol resulting from non-documented unrecorded hypoglycaemic episodes. In one of these patients, hyperinsulinism was accompanied by a low C-Peptide level as may be expected with exogenous insulin administration. There was however, no record of exogenous insulin administration in this patient.

Two patients (numbered 10 and 11 in Table 2) had marked hypocortisolism with suppressed plasma insulin response to hypoglycaemia. Patient numbered 10 was cachectic with exfoliative dermatitis and retroviral negative. He had a suppressed level of plasma IGF-1 at < 20 ug/L with elevated plasma CA-125 level and the possibility of tumour associated hypoglycaemia was considered. We are unable to measure IGF-2 in our laboratory. The low IGF-1 in this patient may be a result of raised IGF-2 with binding of IGF-2 to IGF-1 receptor causing a suppression of IGF-1 secretion via a negative feedback mechanism. The low IGF-1 in patient numbered 10 may also result from possible malnutrition. Computerized scans of the chest, abdomen and pelvis and subsequent Gastro-intestinal endoscopy did not reveal any tumour. This patient had a normal liver function tests result which will argue against chronic liver disease as the cause of very low IGF-1. The episodes of hypoglycaemia in this patient however, abated with subcutaneous octreotide at 100 mcg three times daily. Patient numbered 11 unlike patient numbered 10 (Table 2) was retroviral positive with markedly elevated serum cortisol and suppressed plasma insulin level. It is notable that three non-hyperinsulinaemic patients had adequate plasma cortisol responses despite the presence of tuberculosis and cytomegalovirus infection which are risk factors for hypocortisolism (24,25). Possible explanations include the existence of subclinical hypoadrenalism or cortisol resistance. Four of five patients with satisfactory plasma cortisol response to hypoglycaemia were retroviral positive. Indeed cortisol resistance has been found to be associated with the retroviral infection (26).

It is notable that all the cases of hypoglycaemia that occurred during pregnancy and postpartum were in retroviral positive patients. South Africa has the most number of persons living with retroviral disease, with retroviral disease prevalence of 11.4% (27). Furthermore, 90% of
recent retroviral infections occur in women aged 15-24 years with current pregnancy associated with the highest retroviral disease rates [28]. Retroviral positivity is a major risk factor for hypocortisolism from factors such as cytomegalovirus adrenalitis, tuberculous adrenalitis and ketoconazole therapy for opportunistic infections [24,25,29]. However, in only four of these pregnancies were plasma cortisol levels below 500 nmol/L that is diagnostic of hypoadrenalism. In the other 3 cases, the plasma cortisol levels were above 500 nmol/L suggestive of cortisol resistance, subclinical hypoadrenalism or another unidentified aetiology for hypoglycaemia. The limitations of this study include not measuring plasma levels of ACTH which will assist in the diagnosis of cortisol resistance and sub-clinical hypoadrenalism. The aetiology of hyperinsulinaemic hypoglycaemia could have been further interrogated if plasma levels of sulphonyleureas and insulin antibodies were assessed. Plasma IGF-2 assay is not available in our laboratory. Thyroid function was not measured in our patients, neither was growth hormone assessed during 48 hour fast, therefore the contributory effects of hypothyroidism or growth hormone deficiency in our patients cannot be assessed. However, we have not reported hypoglycaemia in our patients with isolated hypothyroidism.

Conclusions
Majority of our patients admitted with hypoglycaemia were non-hyperinsulinaemic with hypocortisolism as the predominant cause for hypoglycaemia. All pregnancy and post-partum related cases occurred in retroviral positive patients.

Ethics
It was obtained from Ethics Committee Walter Sisulu University.

Authorship Contributions
Concept: Chukwuma Ekpebegh, Dizayn: Chukwuma Ekpebegh Data Collection or Processing: Chukwuma Ekpebegh, Analysis or Interpretation: Chukwuma Ekpebegh, Literature Search: Chukwuma Ekpebegh, Writing: Chukwuma Ekpebegh. Conflict of Interest: No conflict of interest was declared by the authors.

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Hyperglycemia in Hospital: Diagnosis, Classification, Clinical Implications and Treatment

Hastanede Yatan Hastada Hiperglisemi: Tanı, Sınıflama, Klinik Önemi ve Tedavisi

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Abstract
Hyperglycemia is a well-recognized risk factor for hospital-related complications, prolonged stay in the hospital and even mortality. The patients with in-hospital hyperglycemia may be categorized into three groups: i) Patients who have been diagnosed as having diabetes mellitus (DM) before admission; ii) Patients with newly diagnosed DM; and iii) Patients with stress hyperglycemia. The release of stress hormones, such as cortisol, catecholamines, glucagon, growth hormone and the related acceleration in gluconeogenesis and glycogenolysis, medications used for the treatment of primary diseases, such as glucocorticoids and vasopressors, are all claimed to be responsible for the development of in-hospital hyperglycemia. Glucose normalization with insulin therapy has been demonstrated to significantly decrease the morbidity and mortality in all the three groups. Therefore, it is recommended to monitor blood glucose levels for all hospitalized patients irrespective of the accompanying DM diagnosis.

Keywords: Hyperglycemia; hospital; stress

Özet

Anahtar kelimeler: Hiperglisemi; hastane; stress

Introduction
Diabetes Mellitus (DM) is a devastating syndrome that is usually accompanied by co-morbidities, like, cardiovascular disorders, nephropathy, cancer, amputation of the extremities, etc.; all of which enhance the rate of hospitalization by three times than the people with normal glucose homeostasis (1). However, generally, one-third of the affected cases, in a given population, are not even aware that they have diabetes. In a recent retrospective study, 38% of the hospitalized patients exhibited hyperglycemia; 26% of whom had been diagnosed with DM before admission, whereas 12% had no diagnosis (2).

It is a well-known fact that hyperglycemia poses a potential risk for the hospital-related complications, may lead to prolonged hospital stay and may even cause mortality. For a simplified analysis, the patients with in-hospital hyperglycemia may be categorized into the following three groups (3):

i) Patients diagnosed with DM before admission to the hospital;

ii) Patients who do not report DM history, but are found to be hyperglycemic during hospital stay [fasting plasma glucose (PG) ≥ 126 mg/dL and/or random PG ≥ 200 mg/dL] and exhibit persistent hyperglycemia after discharge from the hospital. These patients are considered as newly diagnosed DM cases.

iii) Patients who do not report DM history, but are found to have hyperglycemia during their stay in hospital [fasting PG ≥ 126 mg/dL and/or random PG ≥ 200 mg/dL]. Restoration of normal glucose homeostasis, with any intervention, takes place post hospital dis-
charge. This group is termed as the ‘stress hyperglycemia’ (Table 1).

The tendency of complications and mortality rates are higher among in-hospital patients with newly diagnosed DM and stress hyperglycemia than the others who have known DM. The glucose normalization with insulin therapy has been demonstrated to considerably reduce the mortality and morbidity in all the three hyperglycemic groups. Therefore, it is vital to monitor blood glucose levels of all the hospitalized patients irrespective of the accompanying DM diagnosis.

Hemoglobin A1c (HbA1c) is a valid method for the estimation of mean blood glucose levels within the preceding three months. Thus, this measurement should be performed in all the in-hospital cases with hyperglycemia (4). The HbA1c levels above 6.5% may indicate a diagnosis of DM in the in-hospital subjects. The former helps to discriminate between the unrecognized DM and the stress hyperglycemia. However, it should be noted that the blood loss and transfusion, hemoglobinopathies or hemolytic anemia may interfere with the HbA1c measurements. The diagnosis of diabetes becomes a challenge when the HbA1c levels are either normal or between the 5.6–6.4% range. The workup should be repeated following hospital discharge after the resolution of acute stress (5).

### Mechanisms of hyperglycemia in hospital

The release of the stress hormones, such as cortisol, catecholamines, glucagon, growth hormone and the related acceleration in gluconeogenesis and glycogenolysis, medications used for the treatment of primary diseases, such as glucocorticoids, vasoressors, are all claimed to be responsible for the occurrence of in-hospital hyperglycemia (Figure 1). Glucose elevation in response to the acute disease in patients without any glucose metabolism disorders is known as ‘stress hyperglycemia’ (6). The affected individuals have been shown to have a worse prognosis than the ones with diabetes, normoglycemia or the newly diagnosed diabetes. High glucose, itself, may further lead to clinical deterioration via the impairment of immune functions and aggravated oxidative stress. However, it is not clear whether hyperglycemia, itself, is a marker for poor prognosis or it is a marker for severity of the underlying disease (7).

Under physiological circumstances, normoglycemia is maintained via uptake of glucose in tissues, increase in glycogen synthesis and the suppression of gluconeogenesis in response to the insulin se-

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**Table 1. Classification of hyperglycemia in hospital**

<table>
<thead>
<tr>
<th>Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Known diabetes</td>
<td>Diabetes diagnosed before admission</td>
</tr>
<tr>
<td>Newly diagnosed diabetes</td>
<td>Fasting plasma glucose (PG) ≥126 mg/dL and/or random PG ≥200 mg/dL during hospital stay and confirmed after discharge</td>
</tr>
<tr>
<td>Hospital-related hyperglycemia</td>
<td>Fasting plasma glucose (PG) ≥126 mg/dL and/or random PG ≥200 mg/dL during hospital stay and that reverts to normal range after discharge</td>
</tr>
</tbody>
</table>

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**Figure 1:** Pathogenesis of hyperglycemia in hospital
cotransporting hormone (CRH) and adrenocorticotropic hormone (ACTH) stimulate the secretion of cortisol from the adrenal glands. The proinflammatory cytokines also potentiate the induction of HPA (13).

Pathological conditions, like hypokalemia and pancreatitis, may halt insulin secretion and result in hyperglycemia. Hepatic fibrosis that is observed during cirrhosis may cause hyperglycemia via the prevention of glucose storage. The medications that are used for the treatment of the acute disease may also cause in-hospital hyperglycemia; among which, glucocorticoids are the major ones, owing to their powerful anti-inflammatory properties. These exert diabetogenic effect via promoting gluconeogenesis, peripheral insulin resistance, and the production of free fatty acids. These may increase the risk of diabetic ketoacidosis and hyperglycemic hyperosmolar non-ketotic state for the in-hospital patients. Beta-blockers (metoprolol, propranolol, etc.) may cause hyperglycemia via decreasing the secretion of pancreatic insulin. They may further minimize the peripheral clinical signs of hypoglycemia that may cause fatal outcomes in the unconscious intensive care unit (ICU) patients who have been treated for hyperglycemia. Thiazide diuretics can impair the cellular uptake of glucose and pancreatic insulin secretion. Octreotide, vasopressor agents, and total parenteral nutrition may also cause hyperglycemia in the ICU patients. Quinolone antibiotics (levofloxacin and gatifloxacin) are known to cause hyperglycemia via unknown mechanisms. Calcineurin inhibitors (cyclosporine, sirolimus, and tacrolimus), which are used to prevent allograft rejection, inhibit calcineurin and thereby, the pancreatic beta cell production, which may result in elevated glucose levels in the organ transplant recipients. Protease inhibitors, which are used as antiretroviral agents, are also proposed to decrease insulin sensitivity (14).

Thus, to conclude, it can be stated that there are several underlying diseases and treatment-related contributing factors that cause hyperglycemia in the hospitalized patients.

**Hyperglycemia Among Critically Ill Patients in Intensive Care Units (ICU)**

Hyperglycemia, irrespective of the diabetic status, is a potential risk factor for mortality and morbidity to both medical and surgical ICU patients. Hyperglycemia, with its toxic environment, may worsen the clinical presentation of the underlying disease (2). A retrospective study on 1826 critically-ill general ICU patients, revealed that the mortality rates of normoglycemic cases were lower than the hyperglycemic ones (15). Prognosis is even worse among the ones with stress hyperglycemia (2). In a meta-analysis, the mortality rates of the hyperglycemic ICU patients, who were hospitalized for acute stroke without prior DM diagnosis, were found to be higher (16).

Hyperglycemia may potentiate glucose levels via osmotic diuresis, thereby resulting in decreased glomerular filtration rate (GFR). The latter leads to mitochondrial and endothelial damage via the production of free oxygen radicals and inhibition of nitric oxide (NO), respectively. Hyperglycemia, itself, interrupts immune functions via production of proinflammatory cytokines, increases vascular permeability and activates leukocyte-thrombocyte functions (17). The elevated levels of plasminogen activator inhibitor–1 (PAI–1) and fibrinogen cause thrombocyte aggregation and hypercoagulability. Phagocytosis, chemotaxis and bacterial functions of leukocytes diminish with increasing blood glucose levels (18). Inhibition of collagen synthesis may result in the retardation of wound healing process in patients with hyperglycemia. Overall, if all the interfering factors (as mentioned above) are considered, the diagnosis of diabetes seems difficult in hospital cases. At times, it may become impossible to detect whether the case is of unrecognized diabetes or stress hyperglycemia in critically ill ICU patients. Nevertheless, whatever the case may be, the treatment for hyperglycemic condition must be initiated and the final diagnosis should be postponed, even after the patient’s discharge from the hospital, until complete resolution of the stressful condition is achieved.

**The treatment of Hyperglycemia in general ICUs**

Subcutaneous (SC) insulin injection and oral anti-diabetics are not recommended in critically ill ICU patients, especially those with hypotension and shock. Since the insulin absorption rate cannot be foreseen, thus the risk of hypoglycemia is high among such subjects. Instead, intravenous insulin infusion is considered safer for the ICU patients, who may also have feeding problems. Insulin not only controls blood glucose levels but also lowers the high circulating proinflammatory cytokine levels, thus exerting anti-inflammatory effects (19).

As per the currently available medical literature, various protocols have been described for the infusion of insulin; the different protocols have similar guidelines for hypoglycemia frequency, duration of ICU and total hospital stay, and mortality (20). A clinician may select the most cost-effective protocol for his/her clinic. The paramedical staff must be educated and trained for properly following the chosen protocol. The insulin infusion rate should be corrected with the frequent bedside glucose monitoring in order to avoid hypoglycemia. Serum potassium levels should be checked and replaced wherever required.

In clinics, where intravenous infusion pumps are unavailable, glucose-insulin-potassium may be delivered in the same solution, which is known as the ‘GIK’ solution. Although a tight control of blood glucose has been considered to decrease mortality in critically ill ICU patients, this approach brings the risk of severe hypoglycemia which may also be life-threatening for some patients. The studies that have been performed on coronary ICU patients, among the cases with acute myocardial infarction, have demonstrated that intensive insulin treatment aiming tight glucose control is capable of increasing mortality (21–24). The NICE-SUGAR study, which has compared the effects of tight glycemic control (PG = 81–108 mg/dL) with conventional control (PG < 180mg/dL), among the critically ill patients, has clearly shown that tight control leads to higher life-threatening hypoglycemia and mortality rates. In this high-impact trial, it was recommended that the glycemic targets should be kept in the range which can avoid poor prognosis and hypoglycemia for these cases (25). In another prospective study, conducted on 1548 surgical ICU patients, tight
glucose control was shown to increase mortality and morbidity. The clinical diagnosis of hypoglycemia can be very difficult in these cases, which are generally under sedation and mechanical ventilation. Unrecognized hypoglycemia may cause cardiac arrhythmia, convulsions, and irreversible brain injury (3). Accordingly, glycemic targets should not be kept too low for the critically-ill ICU patients.

Insulin treatment, preferably intravenous insulin infusion, should begin if plasma glucose levels exceed 180 mg/dL in ICU patients. Glycemic targets should be kept between 140–180 mg/dL range. It can be kept between 110–140 mg/dL in some patients, if it does not increase the risk of hypoglycemia (20). Young patients with cardiac surgery, acute ischemic heart, and cerebrovascular disease may benefit from the 110–140 mg/dL targets (3, 26). Plasma glucose levels below 110 mg/dL have been shown to exert additional benefits (3, 25–28).

The patients with diabetes undergo more surgical procedures and the stress caused by the surgeries triggers hyperglycemic state. Perioperative hyperglycemia has been demonstrated to increase morbidity and mortality (29, 30). It is a well-established risk factor for post-operative sepsis and delayed wound healing. Counter-regulatory hormones, released in response to the surgical stress, predispose the susceptible patient to the hyperglycemic condition. Anesthesia, medications, and dehydration due to nausea and vomiting caused by stress-related vagal stimulation may provoke dehydration and worsen the clinical presentation of the afflicted person.

Appropriate medical nutrition therapy to provide sufficient calories, i.e., 15–25 cal/kg/day, is one of the most crucial key points in critically-ill patients. Surgical ICU patients require frequent enteral or parenteral feeding, solutions for which are rich in carbohydrates, thus potentiating hyperglycemia. Moreover, parenteral feeding solutions increase the blood glucose levels via bypassing the intestinal glucoregulatory system (31). Therefore, oral feeding is recommended as early as possible in hospital settings. Plasma glucose levels above 140 mg/dL are considered as a cut-off for initiation of insulin treatment in the ICU patients, who are under parenteral feeding. Insulin may be either added to the daily feeding solutions or given separately using infusion pumps (1). Eighty percent of the total daily insulin requirement may be administered via parenteral feeding solutions as regular insulin. Total daily insulin dose may be given as basal insulin as insulin glargine once daily or insulin Detemir twice daily to those who are fed on continuous enteral infusions. Likewise, similar recommendations may be followed for bolus enteral feeding via nasogastric or gastrostomy. Multiple subcutaneous insulin injections are recommended for the patients who exhibit significant amelioration and can consume oral food under insulin infusion. Nutritional status, accompanying the medications and co-morbidities should be taken into consideration while calculating the SC insulin dose. There are various protocols for the transition from intravenous insulin infusion to multiple SC insulin regimes, as per the currently available medical literature (32, 33). The most commonly recommended protocol is giving 80% of the total insulin infusion dose. Generally, half of the calculated dose is given as basal insulin at once, while the rest of the insulin is divided into three doses and administered as prandial insulin before meals. Basal insulin dosages comprise of insulin glargine, Detemir, and insulin neutral protamine Hagedorn-NPH, and may only rarely be given twice daily. Regular insulin, insulin Aspart, insulin lispro, and insulin glulisine may be chosen as the prandial insulin.

Intravenous insulin infusion should be stopped 1–2 h after the first subcutaneous insulin injection in an attempt to prevent hyperglycemia during follow-up (34). Carbohydrate content of the meals may better be kept stable so as to provide a better glucose control. It is worth noting that the insulin requirement of the patients under glucocorticoid treatment is higher, which should be lowered in parallel to the decreasing glucocorticoid dosages. It has been shown that an exclusive management of in-hospital hyperglycemic patients helps in reducing the duration of hospital stay and the frequency of recurrent hospitalization, along with increased patient satisfaction (35). Thus, it is recommended that the glucose regulation plan should be shaped and updated in parallel to the individual patient requirements, beginning from the admission to discharge from the hospital. Furthermore, appropriate patient treatment regarding medical nutrition therapy, hypoglycemia management, and insulin injection therapy must be properly provided.

**Ethics**

Externally peer-reviewed.

**Authorship Contributions**


Conflict of Interest: No conflict of interest was declared by the authors.

**References**


Genetics of Type 2 Diabetes Mellitus-Asian Perspective (A Review)
Tip 2 Diabetes Mellitusun Genetiği–Asya Perspektifi
(Bir Gözden Geçirme)

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Abstract
Type 2 diabetes mellitus (T2DM) is a metabolic disorder that has come up as a major cause of mortality and continues to cause enormous socio-economic loss across the globe. In the purview of this, a thorough understanding of the pathophysiology, etiology, and pathogenesis of the condition is the need-of-the-hour so as to develop potent therapeutics to have a better control of T2DM. In the developing countries, especially the South Asian region, the condition has become a major health issue owing to the low income and distinct socio-economic patterns. In the European population, a variety of genes have been found to be associated with T2DM; however, their contribution to the other ethnic groups is still unclear. In recent years, various research groups analyzed the prevalence of such genes in Asian populations. The Genome Wide Association Scan (GWAS) successfully identified more than 70 genetic variants that are associated with the T2DM. The present article intends to provide a comprehensive account of the major studies on the genetics of T2DM, with special reference to the Asian population. The various risk factors and the complications associated with the T2DM will be discussed. The review also highlights the major differences and similarities between the susceptibility loci that have been investigated in different ethnicities to provide a novel insight into the disease pathogenesis and its heritability patterns. The information presented, herein, on the genetics of type 2 Diabetes Mellitus holds significance as it paves the way for the development of potential biomarkers and strengthens the fact that specific genetic alterations have important functional roles in the progression or development of T2DM.

Keywords: Diabetes; genetics; genome-wide association scan

Özet

Anahtar kelimeler: Diyabet; genetik; tüm genom bağlantı analizi

Introduction
Diabetes is a prolonged chronic metabolic disorder that has been regarded as the seventh leading cause of death (1). It is expected that about 642 million individuals will acquire diabetes by the year 2040, as per the 2015 atlas of the International Diabetes Federation (IDF). In the developing countries, like, Pakistan, which has a population of 161.66 million, an estimated 6.7 million people get affected with the condition according to the IDF; this figure is expected to increase up to 12.8 million by the year 2035 (1, 2). The
Diabetic Association of Pakistan (DAP) has been involved in conducting national surveys on diabetes and has contributed significantly as the WHO collaborating center for diabetes (3-7). The rapid increase in the prevalence of diabetes is mainly due to the environmental and behavioral changes that may have resulted from the lifestyle changes. The high rates of urbanization have been recorded for Korea, Malaysia, Singapore, Philippines, and Indonesia, while India, Pakistan, China, and Thailand display intermediate rates followed by Sri Lanka and Bangladesh, where urbanization has been slow. Although, diabetes is caused by various factors, however, a sedentary lifestyle remains the major cause. There has been a high incidence of obesity along with diabetes among obese children and women, especially from the South Asian countries. It has been reported that certain genetic factors are responsible for predisposition of South Asians to diabetes, as confirmed from the data on immigrant Pakistani population that demonstrates the association of certain genetic variants with type 2 diabetes (8). Further, an enormously high rate of chronic complications has been linked to diabetes as the latter affects every organ of the afflicted human body, causing chronic diseases, such as retinopathy, neuropathy, nephropathy, and stroke. The situation gets further complicated by the rising prevalence of metabolic syndrome (MS), childhood obesity, and the younger ages of the onset of type 2 diabetes, which is a common occurrence in the developing world, especially, in the South Asian countries.

In view of this, the present review discusses the relevant studies that have been conducted on the Asian population, in order to highlight the genetic basis of the manifestation of the type 2 DM.

Methodology

At first, information was extracted from the evidence-based research studies on ‘genetics of type 2 diabetes’ followed by a specific focus on the ‘genetics of type 2 diabetes in Asia’. The strategies that were employed to search and retrieve the required information are given below:

A. Retrieval of research evidence on ‘genetics of type 2 diabetes’

Database searched for medical research articles

The search for basic research studies on ‘genetics of T2D in Asia’ was initiated by searching the medical research articles indexed in PubMed. It is managed by the National Library of Medicine (NLM) of the US National Institutes of Health and is the world’s largest medical library. PubMed comprises more than 20 million citations for biomedical literature from MEDLINE, life science journals and books that are available online.

Use of citation manager for searching articles

For searching, storing, and sorting the articles, the citation manager software, called the ‘Reference Manager’ was used. The software was also utilized for citation of the articles in the manuscript form.

Method of retrieving research abstracts from MEDLINE

First and foremost, the abstracts were retrieved from MEDLINE by using the two key words: genetics and type 2 diabetes, together using the Booleans logic operator. The retrieval of all the articles having any of the two terms was ensured by using ‘and’ in between the terms. In this way, 19105 articles, which were related to ‘genetics of type 2 diabetes’, were obtained. Another set of articles was retrieved on ‘genetics of type 2 diabetes in Asia’, these articles were screened to specifically suit the purpose for writing this review.

Screening of the retrieved articles

The retrieved 19105 articles were screened for the selection of the articles wherein information about ‘genetics of type 2 diabetes’ was provided. About 1669 articles were filtered that contained data on ‘genetics of type 2 diabetes in Asia’. The articles that presented studies on Asian immigrants were also included. The studies, which demonstrated investigations on diabetes in context to other diseases or testing of nutraceuticals or medicines, were excluded. Further, efforts were made to have access to full texts of as many articles as possible.

To include the recent updates on genetic analyses of type 2 diabetes, information from the relevant websites and reports were retrieved by searching for the basic keywords, ‘diabetes’ and ‘Asia’ (along with other specific terms) using ‘Google’.

Advancement in Genetics of Type 2 Diabetes

The occurrence of T2DM genetic variants differs in various populations and ethnic groups. The identification of these variants among diverse populations has revealed important findings that have contributed toward a better understanding of T2DM at the cellular level. The linkage analysis, candidate gene approach, large-scale association studies, and GWAS have identified more than 70 loci that confer susceptibility to T2DM. Of these, 45 loci were identified in European populations and the other 29 loci were identified in Asian populations, especially, in East and South Asians (Table 1). In order to better understand the pathophysiology of T2DM, immediate benefits were derived from these findings.

Genome Wide Association Scan (GWAS)

The two main approaches to understanding such genes are the candidate gene approach and GWAS; however, the latter, which is able to simultaneously scan several loci in any population, is less expensive and less error-prone (9). GWAS revealed the association of multiple loci with T2DM in geographically different populations, such as Americans, Caucasians, Australians, West Africans and Europeans (10-14). The GWAS studies, on a larger scale, have helped us to investigate the genetic basis of the disease and identified dozens of variants that are associated with the T2DM. However, certain rare variants often remain undetected due to the limitations in genotyping arrays. Still, the best method to detect and identify novel genes in diverse populations remains the GWAS, as it provides more elaborate information on the genetic architecture of disease pathophysiology (15-18).

Although GWAS has greatly improved our understanding towards the genetic basis of T2D, the current genetic risk models for T2D cannot be applied to all populations because most of these studies have been performed in the Europeans. Only limited research studies have been conducted in the South Asians. The discovery of
<table>
<thead>
<tr>
<th>Reference number</th>
<th>Gene/Locus</th>
<th>Gene name</th>
<th>Probable mechanism</th>
<th>Region of gene identified</th>
</tr>
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<tbody>
<tr>
<td>19, 29, 42</td>
<td>PPARG</td>
<td>Peroxisome proliferative activated receptor gamma gene</td>
<td>Insulin action</td>
<td>European</td>
</tr>
<tr>
<td>19</td>
<td>KCNJ11</td>
<td>Potassium inwardly-rectifying channel, subfamily J, member 11</td>
<td>Beta cell function</td>
<td>European/Asian</td>
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<td>Transcription factor 7 like 2</td>
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<td>European/Asian</td>
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<td>Obesity</td>
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<td>ST8GAL1</td>
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<td>GRB14</td>
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<td>Insulin</td>
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<td>CDC123/CAMK1D</td>
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<td>THADA</td>
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<td>Increased insulin resistance</td>
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new loci in different populations is subject to inter-population differences in the allele frequencies and effect sizes. There is growing evidence that the Asian-Indians are at a higher risk for T2D compared to the other populations. Over the years, multiple genes have been successfully identified that contribute to T2D susceptibility. The approaches used include linkage analysis, candidate gene approach, large-scale association studies, and genome-wide association studies (GWAS). In an attempt to minimize the T2D burden, a combined analysis of these loci, such as the construction of genetic risk scores, has to be done for easier and early diagnosis and development of preventive strategies against T2DM.

**Genetics of type 2 diabetes in East Asian population**

As described above, the genetic studies of T2DM in European populations have enormously contributed to our understanding of T2DM susceptibility. However, the existing literature only provides a partial explanation for the heritability of T2DM. It is well known that the discrepancies exist in the allele frequencies and the effect size in different ethnic groups. It is, therefore, important to understand whether such genetic variations are also applicable to the other ethnic populations.

Several research groups have increased the number of confirmed T2DM susceptibility loci to nine (PPAR, KCNJ11, TCF7L2, CDKAL1, CDKN2A/B, IGF2BP2, HHEX/IDE, FTO, and SLC30A8). All these genes may be responsible for affecting the β-cell function, except for the PPAR and FTO, which mainly affects the insulin sensitivity (19, 20). The studies from China, Denmark and few Asian countries revealed that a significant association exists between CDKN2A/2B, SLC30A8, CDKAL1 and KCNQ1 gene polymorphisms with T2DM. A number of GWA studies identified KCNJ11 and TCF7L2 genes as the susceptibility genes for T2DM in Japanese and Chinese populations, respectively. Similarly, previously reported genes from the European population, including the IGF2BP2, HHEX, SLC30A8, CDKAL1, and CDKN2A-B have been detected in populations of Japan, Hong Kong and Korea, of which only CDKAL1 and CDKN2A-B genes show association with the T2DM in Chinese population (21). Prokopenko and colleagues reported that the variants in MTNR1B, influence fasting glucose levels in European population (22). Likewise, KCNQ1 gene has been detected in Chinese population (23); however, IGF2BP2 was not identified as the diabetes susceptibility loci in the latter (24). In comparison to the East Asians, the frequency of genetic variation in TCF7L2 gene has been reportedly higher in Caucasians, Africans and Indians (25). Significant but weak association of FTO variants, on both BMI and T2DM, in East Asian population was identified (26).

**Genetics of type 2 diabetes in South Asian population**

As compared to Europeans, South Asians have approximately six times higher risk of T2DM, as reported in the meta-analysis, which includes the ‘disease-association studies’ (27). A study, involving approximately 41,000 Europeans, showed that the FTO gene polymorphism has significant effects on obesity-related measures and T2DM, as accounted by body mass index (BMI) (28). On the contrary, only a few studies have been reported from the South Asia to highlight the association of FTO gene variants with T2DM and obesity. A study on Sikh population from the Northern India observed the influence of ProAla, IGF2BP2, TCF7L2, and FTO gene variants on adiposity and T2DM (29). Several research studies confirmed FTO as the T2DM susceptibility locus independent of BMI. Further studies among the South Asian population are required to validate these findings (30).

It has been reported that every 10/100 United Kingdom (UK) based South Asians suffers from T2DM (31). In spite of a high prevalence rate of T2DM in the above population, data on the genetic basis of the diseases remains scarce in it. Investigation of genetic variants in the TCF7L2 gene in two South Asian cohorts contributes to the recent efforts in genomics that led to the investigation of potential T2DM susceptibility loci. The two sets of the South Asian population include residents of UK and the Western India; the SNPs investigated were rs7903146 and rs12255372 (32, 33). Two recent studies reported a significant association of TCF7L2 with T2DM while assessing the disease burden in the Indian population (33, 34). Furthermore, two separate studies failed to show any significant association of the Pro12Ala with T2DM in South Indian population of Chennai or in Singapore population. ProAla polymorphism has been reportedly protective against diabetes in Caucasians (35, 36). A multi-centered study, which was conducted in the South Asian individuals in London, Pakistan, and Singapore, revealed the association of six genetic variants at various cytogenetic locations (ST6GAL1, GRB14, HMG20A, VPS26A, HNF4 and AP3S2). Furthermore, ST6GAL1, GRB14 and HNF4A polymorphisms were also associated with impaired insulin sensitivity and altered β-cell function (37). Recently, a meta-analysis of three GWA studies identified six loci (CDC123/CAMKID, THADA, NOTCH2, TSPAN8/LGR5, JAZF1, and ADAMTS9) in Khatri Sikhs in relation to T2DM. The authors observed an association of the only CDC123/CAMKID with T2DM under a dominant model. Moreover, the effect of risk allele associated with this gene was found to be linked with altered β-cell function (38). During T2DM, the FTO expression increases in the muscle that further alters insulin signaling, enhances lipogenesis and ROS production, and also induces mitochondrial dysfunction (39). Another Indian study reported the association of MTNR1B, GCKR, GCK, and G6PC2 gene polymorphisms with abnormal plasma glucose levels as a risk of T2DM and the related metabolic disorders in Asian Indians (40).

The studies conducted on Pakistani population have predicted association of TCF7L2 and SLC30A8, ADCY5 and GLIS3 polymorphisms with T2DM (41). Similarly, recent GWA study investigated around thirty SNPs in two Punjabi populations of Mirpur, Pakistan. The two different populations comprised residents of Azad Kashmir and UK. SNPs within the TCF7L2, PPARG, CDKN2A/2B, FTO, IGF2BP2, HHEX/IDE, KCNQ1, SLC30A8, IRS1, JAZF1, CHCHD9, DUSP9 and KLF14 genes were found to be associated with T2DM (42).

A study conducted in Vietnam reported that the FTO genetic variants are associated with T2DM even after adjustment for age, sex, systolic blood pressure, socioeconomic status, lifestyle factors and obesity-related traits. As per the study, the risk associated with each risk allele of rs9939609 was 1.80-1.92 (43). The variants of RAGE and PAI-1 genes have been shown to be linked with micro- and macro-vascular complications in Caucasians (44, 45). Another study indicated an association of RAGE
and GFPT2 gene polymorphisms with diabetic nephropathy in Indian subjects (46). Similarly, the RAGE polymorphism has been reported to influence diabetic nephropathy, with one of its alleles exhibiting a protective effect against macrovascular complications of diabetes (47). Similarly, a meta-analysis of eight studies showed the protective effect of Pro12Ala polymorphism against retinopathy. A significant association of Ala allele with retinopathy in Caucasians was observed; however, a significant result was observed in association with T2DM and the other related complications. No association of the C677T polymorphism of MTHFR gene was found in Africans, Asians, and Caucasians (48). MTHFR is a gene that is involved in DNA methylation and synthesis along with the regulation of folate activity. It has been reported that the mutant homozygote and heterozygote of C677T polymorphism of MTHFR increases plasma homocysteine that is an important factor leading to diabetic nephropathy (DN).

**Genes associated with type 2 diabetes in non-Asian populations**

With the advent of GWAS, the dissection of the genetic basis for susceptibility to T2D has experienced major breakthroughs in the other parts of the world as well. Grant and colleagues reported the association of TCF7L2 gene variants with T2DM in populations of Denmark, Iceland and United States of America (USA). Moreover, HMG2A and BCL2 genes were also identified as T2DM risk loci in African-Americans and the other multi-ethnic groups, respectively. The study also analyzed the effect of risk alleles of T2DM susceptibility loci in African-Americans, Hispanics, and Asians (49). Previously, genes including TCF7L2, SLC30A8, VPS13C/C2CD4A/8, and ARAP1 have been reported as T2DM susceptibility loci in ancestral Europeans (50). The association between different genes and T2DM has been assessed by systematic reviews and meta-analysis studies. Glutathione-S-transferase including the GSTM1, GSTT1, and GSTP1 are important genes and their association with diabetes has been investigated in two meta-analysis studies (51, 52). Glutathione S-transferase M1 (GSTM1) and glutathione S-transferase T1 (GSTT1) genes are polymorphic in humans and the null genotypes render the enzymes inactive. Several studies assessed the associations between GSTM1/GSTT1 null genotypes and DM risk but demonstrated conflicting results (53), while no significant association was found between GSTP1 and diabetes (51). Further, 1082A/G polymorphism of IL-10 seems to be a risk factor for T2DM in Asians, but not in Europeans or Africans (54).

Among the candidate genes that are related to T2DM, the TCF7L2 exhibits one of the strongest genetic associations with diabetes. In a meta-analysis study after pooling all the data of European, African, and Asian populations, it has been revealed that rs12255372 polymorphism of the TCF7L2 gene, significantly increases the risk of T2DM. In line with such findings, a positive association is observed between rs12255372 and rs7903146 variants of TCF7L2 gene and T2DM in Iranian population (54).

Another study reported that 1082G genotype of IL-10 and 174CC genotype of IL-6 are potential risk factors for T2DM in Egyptians (55). The findings from Pima Indian population suggested that the increased risk of type 2 diabetes was due to the variation within ARHGEF11 gene, which is nominally associated with increased insulin resistance (56). SLC16A11 is identified as a novel candidate gene for type 2 diabetes with a possible role in triacylglycerol metabolism in Mexican and Latin American population (57). The Pro12Ala polymorphism of PPAR was recorded as a protective variant, especially in the Asian population, although the results were highly heterogeneous (58).

It should be noted that the known variants cover only a minuscule amount of the overall estimated genetic heritability; therefore, the complete understanding of the pathogenesis of type 2 diabetes still requires a lot of efforts.

**Conclusion**

Several studies specify that diabetes is a heterogeneous disease. For the discovery of the other genetic susceptibility loci and to further clarify the unclear heritability pattern associated with these complex diseases, investigators should follow the genome-wide approaches, such as GWAS. Employing the techniques for TCF7L2 and FTO, to elucidate the underlying genetic variations, will be crucial for the identification of specific targets for future therapeutic interventions. The contradictory results might be due to the generation of insufficient data; therefore, a more comprehensive approach is suggested for GWAS on specified populations with large sample size.

However, as the disease is multifactorial in nature, the effects of identified genes and pathways on T2D still remain largely unknown. The identification of prognostic and predictive biomarkers seems crucial to understanding the pathogenesis of T2D, as well as the novel therapeutic targets, which in turn should lead to improved outcomes in the affected patients. In contrast to the previous studies, it has been proposed that accumulation of rare variants with mild deleterious effects may substantially increase the relative risk at the individual level. Indeed, with the next generation of sequencing technologies, rare variants may be identified. Such results, together with the known common susceptibility variants, may increase the discriminative value of genetic risk factors and push the limit towards a threshold that may be acceptable for clinical utility.

**Ethics**

Ethical approval was taken from the Institutional Review Board (IRB) of BIDE.

**Authorship Contributions**

Concept: Asher Fawwad and Abdul Basit, Design: Asher Fawwad and Abdul Basit, Data Collection or Processing: Asher Fawwad, Analysis or Interpretation: Asher Fawwad and Rashid Kanza, Literature Search: Rashid Kanza and Asher Fawwad, Writing: Rashid Kanza and Asher Fawwad.

Conflict of Interest: No conflict of interest was declared by the authors.
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Introduction

In peripheral tissues, 5-alpha reductase enzyme converts testosterone into dihydrotestosterone (DHT). DHT is a more potent hormone as compared to testosterone. It is the main hormone which induces the process of masculinity in the male fetus, in the maternal womb and enables the development of external genitalia. In cases of the deficiency of 5-alpha reductase enzyme, this conver-
sion does not take place resulting in ambiguous genitalia in the male fetus. Scrotum, micropenis, and pseudovagina that have not completed their fusion are apparent as labia, clitoris, and normal vagina, respectively (1). A disorder of sex development, 5-alpha reductase deficiency, is a rare autosomal recessively transmitted condition with 46 XY karyotype. It was first defined in a patient with hypospadias, pseudovagina, microphallus, and undescended testicles in 1974 (2). Testosterone allows the differentiation of Wolffian duct, contributing to the formation of vasa deferentia, epididymis, and seminal vesicles. The internal genital organs of patients included in the study were found to be normal. As a result of decreased DHT, the adult patients presented decreased male-type body hair development as well as a sparse beard. Since the enlargement of the prostate is associated with the level of DHT, such patients presented smaller prostates (3). Though these patients have been raised as females; yet, their secondary sexual characters during puberty were towards masculinity under the effect of testosterone hormones, which led to serious psycho-social problems both, in the patient as well as in their parents. 5-alpha reductase has two isoenzymes, one of which is known as “type-1”, which is specific to brain, ovary and the entire skin except for genitalia. Type 2 isoenzyme is only found in the epididymis, seminal vesicles, genital skin, uterus, breast, hair follicle and the placenta. Both type 1 and type 2 isoenzymes exist in the liver, prostate, and testicles. Usually, patients present with a deficiency of type 2 enzyme (4). Numerous genetic mutations involving 5-alpha reductase type 2 enzyme were identified, most of which belonged to the patients with consanguinity.

Material and Method

A group of five male patients who were hospitalized with a pre-diagnosis of disorder of male sexual development and diagnosed with 5-alpha reductase deficiency after assessment between April 2007 and July 2014, were included in the present study after retrospective examination. Patient data were obtained from the hospital and were recorded. Assessment criteria included anamnesis of features of physical examination, laboratory results, karyotype analyses, pelvic monitoring (MRI, USG) and psychiatric history.

Findings

All the patients were males ranging in age between 19 and 24 years, having a mean age of 21.4 ±2.5 (Table 1). However, each of them, having a karyotype of 46 XY, was raised as a female. In all patients, male body structures, enlargement of testis, micropenis or phallus were observed during puberty. In addition, all the patients had hypospadias and blind vaginal pouch. The tendency towards masculinity became more apparent after the end of puberty. All the patients were enrolled to the outpatient clinic for undergoing transsexual surgeries. The DHT levels in these patients were remarkably low. Out of five, three patients belonged to the same family, while the remaining two belonged to another family. Yet, there was first degree of consanguinity in the individuals between these groups, no gynecomastia was found in any of the patients. Ovary or uterus was not found in any of the patients at the time of monitoring. The testicles were mostly within the inguinal channel, except in one patient where testicles were found within the scrotum. All the patients were assessed by a board of psychiatrists. Consequently, all were approved for transsexual surgery after one-year follow-up.

Case Reports

Case 1: A 19-year-old patient dressed in women’s clothing reported to our outpatient clinic for the disorder of sexual development. During the physical examination, male body structure and external genitalia showed ambiguous genitalia. A testicle was present both, at the right inguinal channel and left the inguinal channel, 22x15 mm and 23x16 mm in size, respectively.

Case 2: A 22-year-old patient with feminine appearance reported for transsexual surgery. He had ambiguous genitalia and testicles measuring 27x24x32 mm at the right and 23x28x43 mm at the left side (Figure 1).

Case 3: A 24-year-old patient with feminine appearance reported to our outpatient clinic for transsexual surgery. He had been raised as a female. During puberty, his sex development was towards masculinity. Physical examination revealed microphyns, hypospadias, testicles at labia and pseudovagina (Figure 2). Testicles measuring 27x30 mm at the left side and 19x24 mm at the right side were found at both inguinal channels.

Case 4: A 20-year-old patient with feminine appearance reported to our outpatient clinic for transsexual surgery. He had ambiguous genitalia. Testicles measuring 21x18 mm at the right side and 25x16 mm at the right side, were also present at both inguinal channels.

Case 5: A 22-year-old patient with feminine appearance reported to our outpatient clinic for transsexual surgery. Testicles measur-

<table>
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<tr>
<th>Cases</th>
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<th>Testosterone (2.18-9.05 ng/ml)</th>
<th>T / DHT (3–4)</th>
<th>Bilateral Testicles</th>
<th>Identity/Name/ Karyotype</th>
<th>Uterus/ Ovary</th>
<th>Hypospadias/ Vaginal pouch</th>
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<tr>
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<tr>
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<tr>
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ing 37x24 mm at the left side and 38x21 mm at the right side, were present at both inguinal channels.

Discussion

Testosterone is converted into dihydrotestosterone by the 5-alpha reductase enzyme. DHT, mainly responsible for the development of male external genitalia, enables the enlargement of the phallus, the fusion of labia and growth of the scrotum. These patients were born with an ambiguous genitalia. Afterward, the scrotum appears like labia and the penis like clitoromegaly. Besides this, at various levels, the hypospadias-blind vaginal pouch can also be seen and testicles may remain either in the inguinal channel or within the labia, rarely being in scrotum as well (5). All of the patients had been raised as females due to ambiguous genitalia at the time of birth. 5-alpha reductase deficiency presents with an autosomal recessive transmission pattern. Individuals with this syndrome have normal internal genital organs. Male-type muscle patterns, hair development, voice deepening and spermatogenesis occur during puberty (6). Among the five patients, three patients belonged to the same family, while the remaining two belonged to another family. A first-degree kinship was seen amongst the individuals between these groups. The karyotype in the patients was 46 XY. Due to ambiguous genitalia during delivery, all these patients were raised as females. During puberty, sexual development was towards masculinity. Afterward, these patients underwent transsexual surgeries from femininity to masculinity (7). The common feature of all of these patients is that they have micropenis (8). All patients in the present study also had a micropenis. In some occasions, patients may be thought to be affected by an inguinal hernia during childhood and, in turn, their testes may be surgically removed (9). It is therefore very important for this disorder to be detected during childhood and it must be followed up with a multidisciplinary approach, also involving the parents. Some require surgical intervention and psychotherapy involving the parents. Dihydrotestosterone, the hormone that is usually deficient, may be administered percutaneously (10). Surgical procedures include surgeries of micropenis, hypospadias, undescended testicle, and bifid scrotum (11). Lower levels of DHT in patients with 5-alpha reductase deficiency results in a more viscous as well as decreased volume of semen during ejaculation. Undescended testicles and surgical complications reduce the quality of spermatogenesis, which in turn decreases the likelihood of fertility. Azoospermia and Oligospermia may occur. Yet, early repair of undescended testicles and hypospadias may decrease the risk of such a complication. In patients with a certain level of mutation, spontaneous fertility is sometimes also seen. In some patients, an assisted reproductive technique also successfully incorporates fertility (12, 13). Testosterone levels in these patients were normal though the DHT levels are low.

Conclusion

In the patients with a male disorder of sex development, having low levels of dihydrotestosterone, 5-alpha reductase deficiency should also be considered. The diagnosis, treatment, and follow-up of 5-alpha reductase deficiency involve a multidisciplinary approach.

Ethics

The study has been approved by an institutional Ethics Committee of Dicle University Faculty of Medicine (308/30.07.2015). Informed Consent: Informed consent was obtained from the patients.
Authorship Contributions
Conflict of Interest: No conflict of interest was declared by the authors.
Financial Disclosure: The authors declared that this study received no financial support.

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