

Frequency of distribution of abo and rhesus (Rh) blood group antigens in the female type 2 diabetes mellitus (T2DM) patients in hail region of Saudi Arabia

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Abstract

According to the international diabetes federation (IDF) of Middle East and North Africa region (MENA) about 35 million people have diabetes now and it was responsible for 342,000 deaths in 2015. Over half of those individuals who died were below the age of 60. In Type I diabetes pancreas is unable to secrete insulin, which is a hormone that normally allows cells to absorb glucose from the blood to use for its energy needs. The immune system in the body destroys the cells that are responsible for releasing the insulin, and so eventually no insulin is released at all. Type II diabetes (T2DM) is caused by either due to pancreas not being able to secrete enough insulin, or because our body is not able to use insulin as needed. So insulin resistance seems to be the most common factor for causing the T2DM. If we do not control it now diabetes cases may double to 72 million by 2040. This is an alarming forecast. T2DM is more prevalent in Saudi adult population as compared to the youth population.

Since Saudi Arabia is one of the 19 members of this federation and since cases of diabetes type II (T2DM) are also rising in Saudi population at an alarming rate we decided to look at the correlation between T2DM and the inheritance of ABO and Rh antigens. Our community survey of young female adults (n =394) revealed a high prevalence of T2DM among their adult parents (56.6% of fathers and 50.5% mothers). In comparison T2DM was found to be much less prevalent (4.6%) in Saudi female youth population (average age 22 years).

Our ABO and Rh blood group antigen distribution data among the control female population showed 91.2% to be Rh+ while 8.8% were found to be Rh-. In comparison to control population, among T2DM female patients 95.8% were found to be Rh+ and only 4.21% were Rh-. When compared with the control blood group there was a drastic and statistically significant reduction (at $p < 0.05$) in Rh- blood group individuals among the T2DM female patients (p value 0.043). Similarly, we saw a combined increase in Rh+ individuals among T2DM female patients (95.8%) as compared to the control groups (91.2%). This increase was statistically significant at $p < 0.05$. The Z score was -2.023 and the p -value was 0.043.

Further analysis of our data revealed a moderate but non-significant increase in the expressions of A+, B+ and AB+ antigens in T2DM female patients as compared to the control group. Like male population O+ was the most prevalent blood group among the female control population and the female T2DM patients. However, like male T2DM patients there was a slight yet non-significant decrease in the O+ individuals among the female T2DM patients. At this time the significance of this drastic and significant decrease in the Rh- individual and a moderate decrease in O+ among the T2DM female patients is not clearly understood. Large scale clinical investigations need to be done in order to investigate in depth the reason behind this reduction.

Introduction

According to the world health organization (WHO) globally obesity has doubled between 1980 and 2014. In 2014 about 13% of the global adult population (out of which 11% were adult men and 15% were adult women) was obese. Recently we reported alarmingly high adult obesity rates in Saudi adult population. We found 58.4% of the adults to be obese and 15.84% to be severely obese [1]. Obesity has been linked to more deaths than the underweight population. The main reason for rising overweight and obesity is due to several factors however the major factor is the imbalances between the calories intake and their expenditure (WHO fact sheet June 2016 updates) due to the sedentary habits, poor selection of diet (high fat and the carbohydrate contents) and the lack of exercise by many people. High body mass index (BMI) has been associated with many diseases such as: cardiovascular disease

(stroke and heart disease), osteoarthritis and many types of cancers such as ovarian, breast, liver, prostate, kidney, gallbladder and colon cancers (WHO fact sheet June 2016 updates). Many studies have also linked obesity to diabetes [2,3]. According to the international diabetes federation (IDF), globally there are 415 million people who have diabetes out of which 35.4 million people live in the Middle East

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and the North Africa (MENA) region. Although Saudi Arabia is one of the 19th members of IDF-MENA region, however out of 35.4 million reported diabetes cases in MINA regions, last year approximately 10% (3.4 million) diabetes cases were reported only in Saudi Arabia. This data suggests that diabetes is rising rapidly in Saudi Arabia as compared to many other IDF member countries of MENA region.

Since diabetes is growing rapidly in Saudi population [4] especially in female population [5,6] we decided to investigate possible causes of this rising diabetes. For this study we investigated if there was any association between the inheritance of blood group antigens and the onset of T2DM among the Saudi female population. We recently reported the similar studies on the distribution of ABO and Rh blood group antigens in male non diabetic control and T2DM male patients [4].

Study design

Recently we reported a high prevalence of obesity in Saudi children (male and female) and the adult population [1]. Overweight and uncontrolled obesity is considered as one of the important factors in the rise of T2DM cases globally. In 2015 Fagherazzi *et al.* [7] reported a possible association between the development of diabetes and the ABO and Rh blood groups. Recently we also reported similar studies in the adult Saudi male population (control and T2DM) patients. However, to our knowledge to date no such studies have been done in Saudi adult female T2DM patients. Therefore, in the current study we decided to investigate the possible correlation between the inheritance of blood group antigens (ABO and Rh) among adult T2DM female patients.

We did not use any human or animal tissue samples. Only blood group and HbA1c test result data was collected by 5th year male and female medical students from the local diabetes clinics. Female T2DM patients whose recorded results suggested consistent high fasting sugar levels (hyperglycemia) and high HbA1c levels (above 6.5 mmol/L) were selected for this study. The study plan (combine male and female patients) was previously submitted and approved by the ethical review committee at college of medicine, at university of Hail.

Survey of prevalence of Diabetes in Saudi youth and adult population

We randomly distributed a questionnaire among predominantly young female adults (average age 22, age range 23-29 years) and asked them about their age, family history of cancers, smoking habits, obesity and if they or their parents had diabetes (Type I or type II), and or any other diseases and their responses were recorded. Analysis of our data shows that as compared to the young females (n=394) T2DM was more prevalent in their parents (mother, father or both parents) (Figure 1). Our random community survey also revealed that only 4.6% of our young female subjects had type 1 (data not shown) or T2DM (4.6%). In contrast 91.8% of their parents (at least one or both) were reported by them to be diabetics (Figure 1). Further analysis of this survey revealed that 56.6% of the fathers and 50.5% of the mothers were T2DM patients (Figure 1).

Female T2DM patient average age, age range and HbA1c levels

Since obesity and diabetes are more prevalent in Saudi adult male and female population [1,4] we next looked at the Hb1Ac levels and the blood group antigen distribution among the T2DM female patients who were registered at the diabetes clinic in King Khaled Hospital in city of Hail. Average HbA1c levels in female patients were 12.62mmol/L and the average age of these T2DM patients was 45.9 yrs (Table 1).

Table 1. Average age, age range and the Hb1Ac levels among female T2DM patients.

Average Age and HbA1C levels in Female T2DM Patients			
Genderlevels	Average Age	AgeRange	HbA1c
Female	45.9 yrs	23-87	12.62 mmol/L

There is a lot of debate about the role of diet in causing certain diseases, for example a high fat and high fructose diets has been associated to many disorders such as hepatic and vascular complications and the high risk of diabetes [7], additionally high cholesterol in the diet has also been linked to high risks of colorectal cancers [8]. Similarly, the inheritance of certain blood group antigens has also been associated in causing certain illnesses [9].

Frequency of distribution of ABO and Rh antigens combined, in control non diabetic females and the T2DM female patients

Next we decided to look at the frequency of distribution of ABO and the Rh blood group antigen expression in the control adult female population of Hail region and compared it with the distribution of ABO and Rh antigens in The 2DM female patients that were registered at diabetes clinic at king Khaled hospital in Hail Saudi Arabia. In non-diabetic control female adults, we found 91.2 % to be Rh+ and 8.8% to be Rh- (Figure 2a). In comparison 95.8% of the female T2DM patients were found to be Rh+ while only 4.21% were found to be Rh- (Figure 2b). These results show a 52.2% decrease in the Rh- blood group female T2DM patients (Figure 2b) as compared to the non-diabetic control female population (Figures 2a). These results show a similar reduction in Rh- female T2DM female patients as we recently reported a 3.4-fold reduction in T2DM cases among the Rh negative male adult T2DM patients [4]. We are currently investigating the cause or causes for this dramatic and significant decrease in Rh- male and female T2DM patients as compared to the non-diabetic male and the female control subjects.

Frequency of distribution of ABO and Rh antigens combined, in control non diabetic females and the T2DM female patients

Next we focused our attention towards the distribution of the ABO and Rh antigens among the control non diabetics (Figure 3a) and the T2DM female patients (Figure 3b). Like our male control population [4] out of 91.2% of ABO positive non diabetic females (Figure 2), O+ was the most prevalent blood group (41.7%) and the AB+ was the least prevalent blood group (4.9%) among the female non diabetic community members (Figure 3a). Additionally, 20.8% of the non-diabetic females were A+ while 23.7% of the control population was found to be B+. Just like the male population [4] B+ was the second most prevalent blood group in females (Figure 3a).

Next we looked at the distribution of ABO and Rh antigens in the T2DM female patients registered at the diabetes clinic. Again like control group O+ was the most prevalent blood group in female T2DM patients. However, the percentage of O+ T2DM patients was slightly lower (36.9%), than the control group (41.7%). Similarly, like male patients (Farshori *et al* 2016) AB+ was the least prevalent blood group (7.00%) while B+ was the second most prevalent group among the control (23.7%) and the T2DM (27.1%) female patients (Figure 3b). Further analysis of results showed A+ to be third least prevalent blood group in control (20.8%) as well as in T2DM (24.8) female patients (Figure 3a and 3b).

Change in distribution of ABO and Rh antigens in T2DM female patients as compared to the control non diabetic population.

When we compared the changes in the distribution of ABO and Rh antigens in T2DM female patients as compared to the control

Community Survey of Prevalence of T2DM in Female Youths and their adult Parents

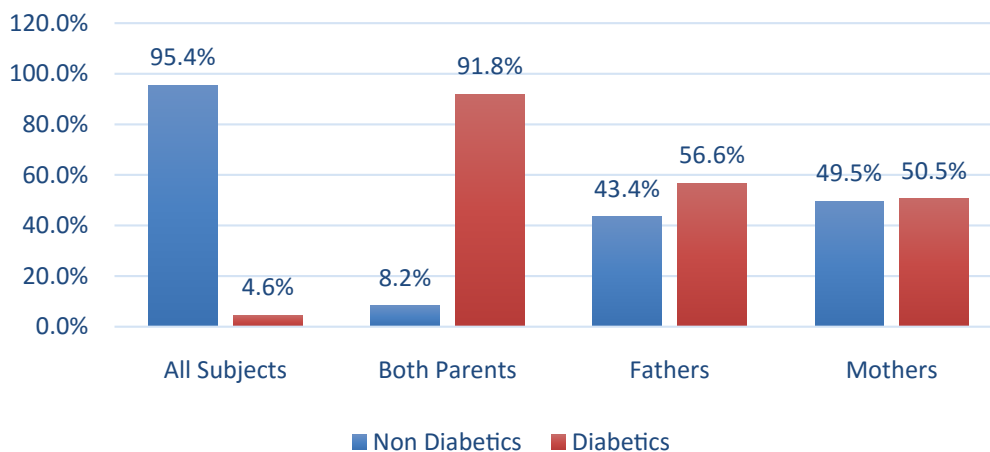


Figure 1. A community survey of prevalence of T2DM among Saudi youths and their parents. Average age of female community members was 22 and age range was 18-38 years.

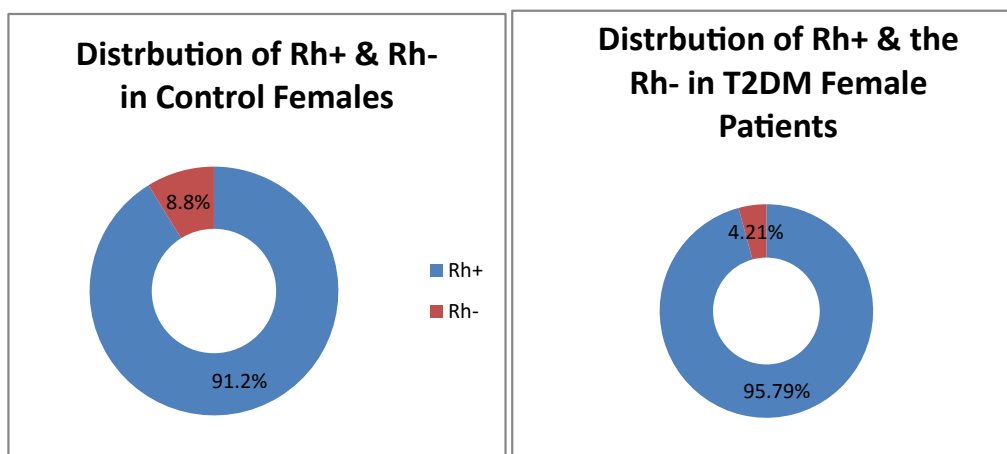
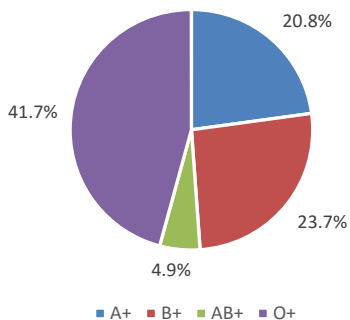


Figure 2. Distribution of ABO and Rh blood group combine in (a) non-diabetic control female and (b) T2DM female population in the Hail region.

Blood Group Distribution Among the Control Non-Diabetic Female Citizens of Hail Region



Blood Group Distribution Among the Female Diabetic (T2DM) Patients of Hail Region

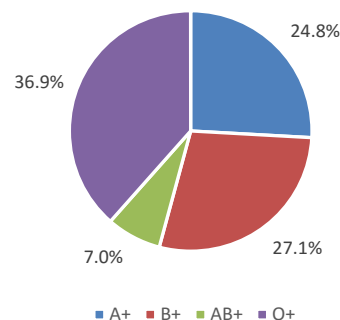


Figure 3. Distribution of ABO and Rh group in (a) non diabetic control female (n 283) and the (b) T2DM female population (n=214) in Hail region.

population we found a similar pattern with moderate increase in the distribution of A+, and the B+ blood groups in T2DM patients as compared to the control population (Figure 4). There was a moderate but non- significant increase in the distribution of A+ among T2DM patients (24.76%) as compared to the control population (20.85%). We saw a similar moderate but statistically non-significant increase in the expression of B+ antigen in T2DM female patients (27.1%) as compared to the control population (23.67%). Although like adult male population [4], AB+ was the least prevalent blood group in the control population (4.95%) and in T2DM patients (7%), however like A+ and B+ blood group there was a non-significant increase in the expression of AB+ antigens among the female T2DM patients as compared to the control population (Figure 4). In summary A+, B+ and AB+ antigens all show a moderate yet statistically non-significant increase in T2DM female patients as compared to the control population (Figure 4). Furthermore, like the male T2DM patients [4], there was a small yet statistically non-significant reduction in the expression of O+ blood group in female T2DM patients as compared to the control population (Figure 4).

Statistical analysis of ABO and Rh distribution in control and T2DM female patients

Statistical analysis of our data using Z-score calculator showed no significant difference in the frequency of distribution of A+ blood type between the non-diabetic female controls (20.85%) and the T2DM female patients (24.8%). The Z score was -1.0352 and the *p*-value was 0.298 at *p* < 0. 05. Thus the A+ antigen distribution results between the control and T2DM female patients were not found to be significantly different. Next we analyzed the distribution of B+ blood group in the control and the T2DM female patients. The Z score was -0.872 and the *p* value was 0.3843. Again the results were not significantly different in T2DM patients (27.1%) as compared to the control group (23.67%). Like A+ and B+ blood type data we saw no significant difference in the distribution of AB+ blood type between the control (4.9%) and the T2DM female patients (7%). The Z value was -0.971 and the *p*-value was 0.332. Therefore, according to our results AB+ distribution was not

significantly different at *p* < 0.05. Next we looked at the distribution of O+ blood types between the controls (41.7%) and the T2DM female patients (36.9%). Although our results show the distribution of O+ to be comparatively lower in T2DM female patients these results are non-significant at *p*- < 0.05 (Z-score 1.078 and the *p* value 0.280).

Finally, we compared the percentage of control non diabetic female in which Rh factor was absent (8.8%) and compared it with the combined T2DM female patients (4.21%). These results were found to be statistically different between the control and the T2DM patients at *p*- <0. 05. The Z score was -2.023 and the *p* value was 0.043. Therefore, in our study like male T2DM patients [4] collectively Rh- is expressed in fewer of the female T2DM patients (4.21% Rh-) as compared to the non-diabetic control group (8.8% Rh-).

In summary the statistical analysis of our blood group distribution data shows a moderate yet a non-significant increase in the expression of A+, B+ and AB+ blood groups and a moderate but statistically non-significant reduction in the expression of O+ antigens in female T2DM patients. However, like male T2DM patients [4] the percentage of female T2DM patients with absent Rh antigens (combined) is significantly less as compared to the control female population. The significance of this drastic reduction in missing Rh antigen is not clearly understood and is currently under investigation.

Discussion

According to the international diabetes federation (IDF) globally there are 387 million people who live with diabetes out of which 37 million live in the MENA region, additionally there were about 199.5 million women who had diabetes and this number expected to rise to about 313.3 million by 2030 (IDF of MENA). IAD further adds that diabetes has been the 9th leading cause of female mortality [10]. According to some estimates diabetes related complications kill more people per year in USA than the AIDS and the breast cancer combined. Some of the most common diabetes related complications include the heart disease and stroke, irreversible kidney damage, the retinal problem and in severe cases the blindness, nerve damage,

A Comparison between the ABO and Rh Antigen Distribution between Control and T2DM Female Patients

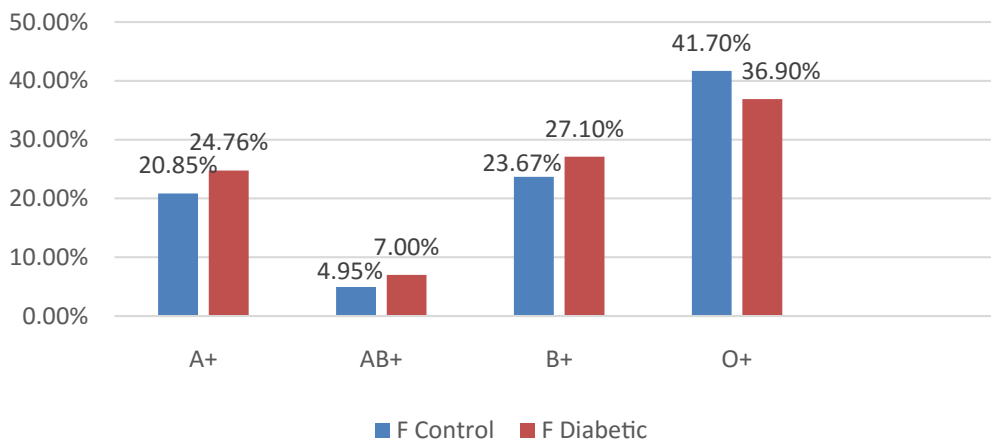


Figure 4. Change in the distribution of ABO and Rh antigens in T2DM female patients as compared to the control non-diabetic population.

poor circulation in the feet and even limb amputations [11] due to uncontrolled hyperglycemia.

According to the earlier studies the prevalence of diabetes in Saudi males was found to be 34.1% and 27.6% in the female population [12]. Previously we also reported a high prevalence of child and adult obesity [1] and the diabetes among Saudi female population of Hail region [5,6]. International diabetes federation predicts that in next 20 years Middle East and the North Africa region will see the greatest increase in the female diabetes population [10]. This prediction made us focus our attention again towards the rising female obesity and diabetes in Saudi population and its probable causes.

In the current study we decided to look at the possible association or the correlation between the inheritance of blood group antigens (ABO and Rhesus) and the development of T2DM in the female population of Hail region of Saudi Arabia. Recently we have published the similar studies for the male population of Hail region [4].

Blood group antigens that we inherit from our parents were first discovered in 1901 by Karl Landsteiner for this important discovery he was awarded a well-deserved Nobel Prize for physiology/ medicine in 1930.

Earlier studies have shown that populations living in different countries [13] and/or living in different regions of the same country [14] tend to differ in the frequency of distribution of ABO and Rh blood group antigens. For example, in earlier studies done on Saudi population by us [4] and by others [15] revealed O+ blood group to be most prevalent at 52%, A+ was expressed in 24% of the population while B+ was expressed in only 17% and only 4% were found to be AB+ in Saudi population. In comparison in the Turkish population 29.8% were O+, 37.8% were A+, 14.2% were B+ and 7.2% of the population was found to be AB+ [16]. The major reason behind these differences is not clearly understood however it is known that one should know his or her blood type before getting any transfusion, surgery and/or an organ transplant.

Results of our random community survey data revealed a high prevalence of diabetes among the adult female mothers as compared to their young female children (Figure 1). This could very well be because of the well informed and well educated young adults who are well aware of consequences that are associated with high obesity and with T2DM and are probably more active in order to avoid getting obese or becoming diabetics. When we looked at the ABO and Rh blood group antigen distribution among the T2DM adult female patients (Figure 3b) and compared it to the control group (Figure 3a) we found a moderate but statistically non-significant increase in the distribution of A+, B+ and AB+ blood group antigens among the female adult T2DM patients as compared to the control group (Figure 4). This data on the female population is slightly different from the male ABO and Rh blood group distribution data among the T2DM patients. While in male T2DM patients we found a statistically significant increase in the B+ blood group individuals [4], but in the current study on female T2DM patients we did not see any significant increase in the distribution of B+ antigens (Figures 3a, 3b and 4). However, like the male T2DM patients, we saw statistically significant decrease in the combined Rh- individuals (4.21%) among the female T2DM patients (Figure 2b) as compared to the combined control female (8.8%) population (Figure 2a). Likewise, when we looked at the combined expression of Rh+ individuals in the ABO blood groups, we found a significant increase in the combined Rh+ antigen distribution (A+, B+, AB+ O+) among T2DM female patients (95.8%) as compared to

the control (91.2%) population. The Z test revealed the results to be significant at $p < 0.05$. The significance of this increase in combined expression of Rh+ individuals among female T2DM patients and the drastic and statistically significant reduction in the missing Rh antigen is not clear and is currently under our investigation.

Study limitations

Current study was conducted with a small number of female subjects that were available in the Hail city. We randomly collected data from 490 control subjects (283 were females and 207 were males) and compared it with a total of 342 T2DM patients out of which 214 were female patients and 128 were male patients. For each female T2DM patient we collected only the first reading of HbA1c levels that were available at the diabetes clinic.

Conclusion

In conclusion our data analysis shows a moderate and statistically non-significant increase in the distribution of A+, B+ and AB+ blood groups and a moderate yet statistically non-significant reduction in the distribution of O+ blood groups among the T2DM female patients. Our results are in agreement with the studies published earlier (Rao and Shetty 2014) in that the expression of O blood group is significantly high and the AB is significantly low in comparison to other blood groups in Saudi population (diabetic or non-diabetics). Additionally, like male T2DM patients we found a statistically significant decrease in the combined Rh- female T2DM patients (4.21%) as compared to the combined control female population (8.8%). Currently large studies are underway to further investigate the possible correlation between the ABO and Rh antigen and the development of T2DM.

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