High Incident Type 2 Diabetes Mellitus among Patients with Essential Hypertension

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Abstract—Obesity increases the risk for diabetes, but there is limited evidence for this relationship among patients with hypertension. A retrospective cohort study was undertaken between 1/10/2013 and 30/9/2017. It included patients with hypertension visiting primary health care centres located in Qatif Province, Saudi Arabia. It included 438 patients (234 obese and 204 non-obese) with normal or prediabetic levels of fasting blood glucose and/or haemoglobin A1c at baseline. The incidence of type 2 diabetes per 1,000 person-years among obese and non-obese groups was 100.7 (95% confidence interval: 79.5-125.9), and 63.8 (95% confidence interval: 46.7-85.1) respectively. Median follow-up duration was 38.3 months. Yearly incidence of diabetes was the highest in the first two years of follow-up among obese and non-obese groups, and thereafter remained high only in the obese group. Predictors of type 2 diabetes development included being female, having a family history of diabetes, having a dyslipidaemia, higher fasting blood glucose level per mg/dl, and higher body mass index per kg/m². The result showed high incidence rates of diabetes among hypertension patient and was particularly profound among patients who are obese. Primary diabetes prevention program is in need in this country.

Index Terms—hypertension, obesity, dyslipidaemias, diabetes mellitus, type 2

I. INTRODUCTION

The prevalence of diabetes has been markedly high all over the world in recent years [1], [2]. Saudi Arabia is one of the top countries with regard to the prevalence of diabetes [3]. This can be attributed to rapid urbanization, and noticeable changes in human behaviour including use of technology, sedentary lifestyle, and high caloric food intake [4]. Consequently, high Body Mass Index (BMI) emerged as a major health problem affecting every two out of three Saudi adults [5]. It was considered the first leading risk factor for disability-adjusted life years [3]. Due to the prevalence of high BMI, type 2 diabetes mellitus (T2DM) and hypertension became major public health problems [6]. These issues exert major strains on the national health system and call for urgent employment of preventive measures [7], [8].

There is a scarcity in literature on the incidence of new-onset T2DM, particularly among patients with hypertension in Saudi Arabia [9]. Additionally, behavioural, genetic, and environmental predictors [10] for new onset T2DM have not yet been determined for Saudi patients with hypertension. This study was designed to determine the incidence rate, yearly incidence, and the predictors for new-onset T2DM development among Saudi patients diagnosed with essential hypertension.

II. METHODS

A. Setting and Procedure

This retrospective cohort study was conducted at all nine urban Primary Healthcare Centres (PHCs) in Qatif Province, Saudi Arabia. Urban PHCs were selected for logistical convenience. PHCs in Saudi Arabia, including the Qatif PHCs, provide most primary healthcare services, including those for chronic diseases [11]. This is delivered at PHCs through a team consisting of a physician, a chronic disease nurse, and occasionally a dietitian, along with referrals to other specialties if required [12]. All laboratory services are delivered through one central laboratory.

Data of patients with chronic diseases were presented on electronic and paper-based medical records. Only patients who followed-up on chronic disease care were registered in the electronic medical records. Participants were primarily selected based on the electronic medical records, and whether they met inclusion and exclusion criteria of the study. Electronically unavailable data were collected from paper-based records (which were more complete). Chronic disease nurses were contacted for supporting information when needed. Baseline data were collected for each participant on the recruitment date 1/10/2013. Data that was unavailable at date of recruitment were collected from six months before the date of recruitment, and if not found, they were collected from six months after the date of recruitment. Data of each participant were completed follow up through electronic medical record for up to four years, until one of the following occurred:
(1) Development of T2DM as defined in this study (see T2DM definition below), even if the participant died later in the study period.

(2) No development of T2DM by the end of the study’s four-year follow-up period: ending on 30-9-2017.

As this is a retrospective study used secondary data, no consent was obtained from the participants. However, the data were collected anonymously as no names were collected and the data were stored directly into a laptop with personal password. The study protocol was approved by the institutional review board of the Saudi ministry of health (1439-26879).

B. Study Population

Cluster sampling technique was used to select 438 eligible participants (about 8.96% of the registered patients with essential hypertension as of the date of recruitment at the selected PHCs). Patients ≥ 18 years of age, who were diagnosed with essential hypertension, had normal or prediabetes level of Fasting Blood Glucose (FBG) level and/or Hg A1c percentage, had complete follow-up data during the study period, and were not diagnosed with type 1 or type 2 diabetes mellitus, nor were on oral hypoglycaemic agents, were eligible to participate. Patients who died before completing the four-year period of follow-up sessions and did not develop T2DM were excluded from the study.

C. Definitions

Patients were considered as experiencing essential hypertension and dyslipidaemia if their medical file indicated they were diagnosed by their primary treating physician. Physicians are trained to diagnosis hypertension according to the Saudi hypertension society guidelines [12].

BMI was defined as a person's weight in kilograms divided by his/her height in meter square (kg/m²). Standards of the Centres of Disease Control and Prevention for BMI were used for weight classification [13]. The patients were classified as an unexposed group when their BMI was below 30.0 kg/m², and exposed group when their BMI 30.0 kg/m² and above.

The diagnosis of T2DM was based on American Diabetes Association’s 2016 criteria [14]. Based on these criteria, patients were considered to have normal blood glucose level when their haemoglobin A1c percentage was ≤ 5.7% and FBG < 100 mg/dl. Patients were considered to have pre-diabetes when their haemoglobin A1c percentage was between 5.7-6.4% or FBG between 100-125 mg/dl. Patients were considered to have diabetes when their haemoglobin A1c was ≥ 6.5% or FBG ≥ 126 mg/dl or when they were using anti-diabetic medication.

D. Statistical Analysis

Statistical Package for Social Sciences (SPSS) version 20 was used for statistical analyses. Baseline data was presented in descriptive statistics using numbers and percentages for categorical variables and median ± Interquartile Range (IQR) for contentious variables. Descriptive statistics were calculated for whole, obese, and non-obese groups. A P-value of <0.05 (two-tailed) was chosen as level of significance. Mann-Whitney test was used for continuous data and χ² test for categorical data, to represent the difference between obese and non-obese groups for each variable.

Observation time was calculated as the interval between the date of recruitment to T2DM development or end of follow-up period at fourth year. The 4-year incidence rate of T2DM and the 95% Confidence Interval (CI) were calculated per 1000 person-years by dividing the number of participants who developed T2DM during follow-up as numerator, and total person-time as the denominator. Cumulative hazard curves were displayed along with Log-Rank test using Kaplan-Meier survival analysis. Associations with new-onset T2DM were analysed using Cox proportional hazards models.

Nine baseline variables thought to be associated with new-onset T2DM were tested using Cox regression models, with and without interaction terms. The results were presented as Hazard Ratio (HR) with 95% confidence intervals. These variables included sex (female vs. male), age, smoking status (yes vs. no), BMI, systolic blood pressure, diastolic blood pressure, dyslipidaemia diagnosis (yes vs. no), family history of diabetes (yes vs. no), and Fasting Blood Glucose (FBG).

III. Results

Baseline sociodemographic characteristics according to obesity status are presented in Table I. At baseline, 234/438 (53.4%) patients with essential hypertension were obese.

Cumulative incidence of new-onset T2DM for the four years of follow up was 26.5% [31.2% obese and 21.1% non-obese]. Per 1000 person-years, 82.9 (95% CI: 68.8-99.1) new-onset T2DM occurred in whole cohort, 100.7 (95% CI: 79.5-125.9) occurred in the obese group, and 63.8 (95% CI: 46.7-85.1) in the non-obese group [age adjusted HR = 1.59, 95% CI: 1.07-2.34]. Per 1000 person-years, 53.0 (95% CI: 29.5-88.4) new-onset T2DM occurred in obese male, and 55.7 (95% CI: 33.0-88.5) in non-obese male [age adjusted HR = 1.04, 95% CI: 0.47-2.27]. Per 1000 person-years, 125.1 (95% CI: 96.3-159.9) new-onset T2DM occurred in obese female, and 69.8 (95% CI: 46.9-100.1) the non-obese female [age adjusted HR = 1.70, 95% CI: 1.07-2.70], as shown in Table II.

Yearly cumulative incidence of new-onset T2DM was high for both obese and non-obese groups and was not significantly different in the first and second years (P-value=0.289 and 0.536 respectively). This difference was significantly higher among obese group compared to non-obese group in the third year (P-value=0.035). This difference was not significantly different for the fourth years (P-value=0.207). P-value for four years trend=0.439 (see Table III).
TABLE I. **SOCIODEMOGRAPHIC CHARACTERISTICS ACCORDING TO OBESITY STATUS**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Whole N (%)</th>
<th>Obese N (%)</th>
<th>Non-obese N (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number (%)</td>
<td>438 (100.0)</td>
<td>234 (53.4)</td>
<td>204 (46.6)</td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>156 (35.6)</td>
<td>72 (30.8)</td>
<td>84 (41.2)</td>
<td>0.023</td>
</tr>
<tr>
<td>Female</td>
<td>282 (64.4)</td>
<td>162 (69.2)</td>
<td>120 (58.8)</td>
<td></td>
</tr>
<tr>
<td>Median age in years (IQR)</td>
<td>53 (45.0-61.0)</td>
<td>56 (46.3-66.0)</td>
<td>52 (44.8-57.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Completed highest level of education</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than primary school</td>
<td>182 (41.6)</td>
<td>82 (35.0)</td>
<td>100 (49.0)</td>
<td>0.003</td>
</tr>
<tr>
<td>Primary school and above</td>
<td>256 (58.4)</td>
<td>152 (65.0)</td>
<td>104 (51.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Marital status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Currently not married</td>
<td>96 (21.9)</td>
<td>52 (22.2)</td>
<td>44 (21.6)</td>
<td>0.869</td>
</tr>
<tr>
<td>Currently married</td>
<td>342 (78.1)</td>
<td>182 (77.8)</td>
<td>160 (78.4)</td>
<td></td>
</tr>
<tr>
<td><strong>Main work status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employed</td>
<td>140 (32.0)</td>
<td>68 (29.1)</td>
<td>72 (35.3)</td>
<td>0.163</td>
</tr>
<tr>
<td>Unemployed/Retired</td>
<td>298 (68.0)</td>
<td>166 (70.9)</td>
<td>132 (64.7)</td>
<td></td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>89 (20.3)</td>
<td>44 (18.8)</td>
<td>45 (22.1)</td>
<td>0.151</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>51 (11.6)</td>
<td>22 (9.4)</td>
<td>29 (14.2)</td>
<td></td>
</tr>
<tr>
<td>Never smoke</td>
<td>298 (68.0)</td>
<td>168 (71.8)</td>
<td>130 (63.7)</td>
<td></td>
</tr>
</tbody>
</table>

IQR: interquartile range

TABLE II. **INCIDENCE OF TYPE 2 DIABETES MELLITUS ACCORDING TO OBESITY STATUS**

<table>
<thead>
<tr>
<th>Type 2 diabetes mellitus</th>
<th>Whole N (%)</th>
<th>Obese N (%)</th>
<th>Non-obese N (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number (%)</td>
<td>438 (100)</td>
<td>234 (53.4)</td>
<td>204 (46.6)</td>
<td></td>
</tr>
<tr>
<td>Number developed T2DM (%)</td>
<td>116 (26.5)</td>
<td>73 (31.2)</td>
<td>43 (21.1)</td>
<td>0.017</td>
</tr>
<tr>
<td>Median duration of follow up in months (IQR)</td>
<td>45 (40.8-47)</td>
<td>46 (42.3-47)</td>
<td>45 (30.8-46)</td>
<td>0.018</td>
</tr>
<tr>
<td>Person-years</td>
<td>1399.3</td>
<td>724.9</td>
<td>674.4</td>
<td></td>
</tr>
<tr>
<td>Incidence rate per 1000 person-years (95% CI)</td>
<td>82.9 (68.8-99.1)</td>
<td>100.7 (79.5-125.9)</td>
<td>63.8 (46.7-85.1)</td>
<td></td>
</tr>
<tr>
<td>The hazard ratio (95% CI) adjusted for age</td>
<td>1.59 (1.07-2.34)</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hazard ratio (95% CI) adjusted for age and sex</td>
<td>1.48 (1.001-2.19)</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Male N (%) | 156 (100) | 72 (46.2) | 84 (53.8) | 0.874 |
| Number developed T2DM (%) | 29 (18.6) | 13 (18.1) | 16 (19.0) |         |
| Person-years             | 532.7      | 245.3      | 287.4      |         |
| Incidence rate per 1000 person-years (95% CI) | 54.4 (37.2-77.2) | 53.0 (29.5-88.4) | 55.7 (33.0-88.5) |         |
| Hazard ratio (95% CI) adjusted for age | 1.04 (0.47-2.27) | Reference |         |

| Female N (%) | 282 (100) | 162 (57.4) | 120 (42.6) | 0.009 |
| Number developed T2DM (%) | 87 (30.9) | 60 (37.0) | 27 (22.5) |         |
| Person-years             | 866.7      | 479.7      | 387.0      |         |
| Incidence rate per 1000 person-years (95% CI) | 100.4 (80.9-123.2) | 125.1 (96.3-159.9) | 69.8 (46.9-100.1) |         |
| Hazard ratio (95% CI) adjusted for age | 1.70 (1.07-2.70) | Reference |         |

CI: confident interval. IQR: interquartile range. T2DM: type 2 diabetes mellitus

Fig. 1 illustrates that cumulative hazard for new-onset T2DM was higher in the obese group as compared to the non-obese group, and the difference was statistically significant (P = 0.017).

The Fig. 2 illustrates that cumulative hazard for new-onset T2DM based on obesity status at baseline was significantly different among women but not men [P = 0.013 and 0.951 respectively]. Further, it was significantly different in the younger group (less than 60 years old) but not in the older group (60 years and above) [P = 0.017 and 0.839 respectively]. The association of incident new-onset T2DM with obesity was not affected by interactions related to sex (P = 0.416) or age categories (P = 0.393).
Fig. 2 illustrates the multivariate analysis and showed that female sex, family history of diabetes, dyslipidaemia, higher FBG level per mg/dl and higher BMI per kg/m² were independently associated with progression to T2DM.

Fig. 3 illustrates the multivariate analysis and showed that female sex, family history of diabetes, dyslipidaemia, higher FBG level per mg/dl and higher BMI per kg/m² were independently associated with progression to T2DM.

IV. DISCUSSION

In this study, 53.4% of participants were obese at baseline. T2DM incidence was 82.9/1000 person-year, 100.7/1000 person-year in the obese group and 63.8/1000 person-year in the non-obese group. Yearly incident T2DM was high in all follow-up years in the obese group, but only in the first two years in the non-obese group. Women, those with family history of diabetes, those with dyslipidaemia diagnosis, higher FBG level per mg/dl, and higher BMI per kg/m² were associated independently with incident T2DM.

To the best of our knowledge, this is the first study quantifying the incidence rate, yearly incidence, and predictors of T2DM in patients with essential hypertension in Saudi Arabia. The measured T2DM incidence among patients with essential hypertension and obesity in the present study was high compared to the reported T2DM incidence rates from different countries by different authors regardless of the baseline characteristics of the participants [15]-[19]. However, including only high-risk hypertensive patients with other comorbidities may explain this finding [18].

Nevertheless, the high incidence of T2DM may reflect the high prevalence of diabetes in this country [2] which may be associated with rapid epidemiological and nutritional transitions [21]. It may also reflect an aggressive pathophysiological process of T2DM among these patients, which may be related to genetic predisposition. Literature reports a high level of resistin among Saudi population [22]. Resistin is a signalling molecule released by adipose tissue, leading to increased insulin resistance, and high insulin and blood glucose levels [23].
We found a higher incidence rate of T2DM among the obese group and female. Obesity is a well-known risk factor for T2DM development [24]. However, national and international studies have found a higher incidence of T2DM among male as compared to female in the general population [16], [18], [25]. The higher incidence of T2DM among female in this study may be related to their reproductive stage in life, as the mean age was around the menopausal stage. Female undergo several hormonal changes during and after menopause, including decrease in oestrogen and increase in testosterone levels, and an increase in visceral obesity, which are risk factors for chronic diseases including diabetes [26], [27]. On the other hand, if we compare the higher T2DM prevalence among male in previous Saudi studies [2], [28] with the quantified higher incidence rate among female in this study, it could be attributed to the higher mortality from essential hypertension comorbid with T2DM among female.

The subgroup analyses indicated that obesity predicted T2DM among female but not male, and among the younger group but not the older group. In general, evidence demonstrated that lifetime risk for diabetes decreased with advancing age [29] but increased among female of all ages [30]. Therefore, primary prevention of T2DM comorbidity with essential hypertension should be focused around these target groups.

Further, the first two years of follow-up had the highest incidence rate for T2DM among whole, obese, and non-obese groups with essential hypertension; but after two years, high incidence rate continued for the obese group only. Similarly, the T2DM conversion rate was the highest in the first two years, and it was more among the non-obese group than the obese one. Therefore, management plan of patients with essential hypertension to prevent comorbidity with T2DM should be started in the first two years of follow-up regardless of the obesity status, and the effort should be continued for those with obesity.

The current study found an independent association between BMI and T2DM among patients with essential hypertension, which was in trend with past research with the general population [31], [32]. However, research has shown that losing weight through a combination of diet and physical activity can prevent T2DM within the high-risk population [33], [34]. The epidemic state of T2DM and obesity in this country calls for an urgent national diabetes prevention program, particularly for high-risk patients with hypertension, to improve their quality of life [35].

Baseline blood glucose is an independent risk factor for progression to T2DM in general [29], [36]. This is also true for patients with essential hypertension, where we found that baseline FBG level was the most significant independent predictor for new-onset T2DM. Moreover, our results indicated that T2DM risk could be present even with normal FBG level in patients with essential hypertension. Similar relation were also found in VALUE study, where increased FBG level represent an independent risk factor for T2DM in patients with hypertension [37]. Therefore, preventive efforts for T2DM among this cohort should be initiated even before reaching abnormal level of FBG.

Furthermore, an independent association between female and new-onset T2DM was observed. This might be explained by a tendency for female to experience clusters of risk factors for T2DM, as compared to male. These include obesity, age-related increase in waist circumference, metabolic syndrome, gestational diabetes, lower socioeconomic status, psychosocial and work stress, inactivity, eating an unhealthy diet, and even genetics [38]. For instance, Saudi female tend to be more physically inactive, eat more unhealthy food, experience obesity to a greater extent, and have a lower socioeconomic status as compared to Saudi male [5], [39], [40]. In addition, they have a high prevalence of gestational diabetes [2].

We also found an independent association between family history of diabetes in first degree relatives and new-onset T2DM development and this association too was detected in previous researches [41]. In Saudi Arabia, this association might be explained by high rate of consanguinity [42].

Lastly, we found an independent association between dyslipidaemia and T2DM in patients with essential hypertension. Other studies have indicated that different types of dyslipidaemia can predict T2DM [17]. This occurs through the accumulation of cholesterol on β-cells and impaired insulin secretion [43].

This retrospective study was based on pre-collected data for non-research purposes, and therefore suffered from missing data and possible missing risk factors for incident T2DM. However, identifying these aspects can provide opportunity to improve hypertension care in Saudi Arabia. Further, changes in time-varying predictors were not considered during measurement or analyses. This study was based on residents of urban communities in Qatif Province, and caution should be taken when generalizing the results to the Saudi population as a whole.

V. CONCLUSION

In conclusion, Saudi patients with essential hypertension have one of the highest incidence rates of T2DM in the world. Annual risk of new-onset T2DM was the highest in the first two years of follow-up, particularly among patients who are obese. Obesity contributed to T2DM in young populations and female. Primary diabetic prevention program targeting modifiable risk factors, namely high BMI, in high-risk hypertensive patients is is need in Saudi Arabia, a country facing diabetes epidemic. Further research studies the epidemiological trend in T2DM from the national registry with a particular focus on demographics, prevalence, newly-diagnosed cases, and comorbidities is suggested. Furthermore, Study the influence of body fat distribution on T2DM development may clarify more the association between obesity and diabetes.
CONFLICTS OF INTEREST
The authors declare no conflict of interest.

AUTHOR CONTRIBUTION
Ghadeer Al-Ghareeb conducted the research, wrote the paper; Hayfaa Wahabi planned the research; Bader Almustafa conducted the research; Amel A. Fayad analysed the data; all authors had approved the final version.

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REFERENCES


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