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Diabetes Mellitus: Findings from 20 Years of the Tehran Lipid and Glucose Study

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Abstract

Context: We summarized findings from Tehran lipid and glucose study (TLGS) about different aspects of type 2 diabetes (T2D) over the span of nearly 2 decades.
Evidence Acquisition: A review was undertaken to retrieve papers related to all aspects of T2D from the earliest date available up to January 30, 2018.
Results: An annual crude incidence rate of 10 per 1000 person-years of follow-up was found for T2D in adult participants. Overall incidence rate of pre-diabetes/T2D was 36.3 per 1000 person-years or about 1% each year among youth. Diabetes was associated with increased risk of CVD [hazard ratio (HR): 1.86, 95% confidence interval (95% CI): 1.57 - 2.27] and mortality [HR: 2.56; 95% CI: 2.08 - 3.16] in the total population. Compared with non-diabetic men and women, their diabetic counterparts survived 1.4 and 0.7 years shorter, respectively, during 15 years of follow-up. Wrist circumference, hyperinsulinaemia, 25-hydroxy vitamin D and increase in alanin aminotranferase provided incremental prognostic information beyond the traditional risk factors for incident T2D in adults. Using decision tree algorithms, a number of high risk groups were found for incident T2D. A probability of 84% was found for incidence of T2D among a group of men with fasting plasma glucose (FPG) > 5.3 mmol/L and waist to height ratio (WHtR) > 0.56, and women with FPG > 5.2 mmol/L and WHtR > 0.56.
Conclusions: Original TLGS studies have contributed greatly to clarify important evidence regarding the epidemiology and risk factors for T2D among Iranian population.

Keywords: Diabetes, Tehran Lipid and Glucose Study, Cardiovascular Disease

1. Context

Diabetes is a common chronic disease worldwide (1). An estimated 415 million people globally had diabetes in 2015, a rate projected to increase to 642 million people by 2040, with most having type 2 diabetes (T2D) (2). Diabetes poses an increased risk of mortality and morbidity among those who already have it (3). A total of 56.4 million deaths occurred worldwide in 2015, of which, 1.6 million (2.8%) were due to diabetes (4). The Eastern Mediterranean Region (EMR) has the highest prevalence of diabetes in the world, a figure projected to increase in the near future (5, 6). Before the year 2000, a high prevalence of diabetes had been reported in some urbanized populations of Iran (7, 8). In 2005, the first survey of risk factors of noncommunicable diseases of Iran, conducted on 70.981 populations aged 25 - 64 years, found that about 2 million Iranian adults (7.7%) had diabetes, about half of them were undiagnosed; moreover, an additional 16.8%, or 4.4 million, had impaired fasting glucose (IFG) (9).

In 1999, the Tehran lipid and glucose study (TLGS), as the first population based cohort in Iran, was initiated to investigate diabetes, hyperlipidemia, hypertension, obesity, cigarette smoking and other cardiovascular risk factors among a representative population of Tehran, the capital of Iran (10). The prospective observations made over the course of nearly two decades of follow-up have clarified important knowledge regarding the epidemiology and risk factors for diabetes. A large number of investigators from around the Iran have worked with TLGS data and published many articles since 2000. This review briefly presents the key findings from those papers and summarizes several contemporary TLGS publications on different

aspects of T2D.

2. Evidence Acquisition

We searched PubMed, Scopus, Web of Science, and Google Scholar for all relevant studies from the earliest available date to January 30, 2018. The search query included three keywords (diabetes, TLGS and Iran) which were combined with "and".

3. Results

We found a total of 22 articles for inclution in our review. A summary of the findings of the included studies is presented below.

3.1. Prevalence

3.1.1. Youth

Of a total of 3,721 residents aged 10 - 19 years from first and second phases of TLGS, 8 people were diagnosed with type 1 diabetes (T1D) or T2D (11).

3.1.2. Adults

According to data from phase 1 of TLGS (1999 to 2001), among 9,489 Iranian adults aged $\geq$ 20 years, the prevalence of diagnosed and undiagnosed T2D were 8.1% and 5.1% in males, and 10% and 4.7% in females, respectively. Also, the prevalence of isolated IFG [fasting plasma glucose (FPG) of 5.6 - 6.9 and 2-h postchallenge plasma glucose (2h-PG) < 7.7 mmol/L], isolated impaired glucose tolerance (IGT) (2h - PG 7.7 - 11.0 and FPG < 5.6 mmol/L) and combined IFG/IGT were 8.7%, 5.4% and 4.0% in males, and 6.3%, 7.6%, and 4.5% in females, respectively (12).

3.2. Incidence

3.2.1. Youth

During 1999 to 2011, with median of 9.2 years of follow-up, 208 cases of pre-diabetes/T2D occurred among 2,563 subjects, aged 10 - 19 years. Accordingly, overall incidence rate of pre-diabetes/T2D was 9.1 per 1000 person-years or about 1% each year among Iranian youth, aged 10 - 19 years (11).

3.2.2. Adults

During 1999 to 2011 (median follow-up of 9.5 years), among 8,400 (3,620 men) non-diabetic participants of TLGS, an estimated 736 people (433 women and 303 men) > 20 years of age were newly diagnosed with T2D. In the total population, the annual crude and age-standardized incidence rates (95% CI) of T2D were 10.6 (9.92 - 11.4) and 9.94 (7.39 - 13.6) per 1000 person-years of follow-up. The corresponding values were 10.2 (9.13 - 11.4) and 9.36 (5.84 - 14.92) in men, and 11.0 (9.99 - 12.0) and 10.1 (7.24 - 13.9) in women, respectively. The highest incidence rate of T2D was found in men over the age of 80 years (21.8 per 1000 person-years) and women aged 60 - 69 (24.0 per 1000 person-years) (13). In addition, during 1999 to 2012 (median follow-up of 9.5 years), an estimated 1,755 people (853 men and 902 women) > 20 years of age were newly diagnosed with pre-diabetes (combined IFG/IGT, isolated IFG and isolated IGT), with incidence rates of 46.1 and 36.8 per 1000 person-years in males and females, respectively (14).

3.3. Risk Factors

3.3.1. Youth

Multivariate analysis of data from the TLGS found that one standard deviation (SD) increase in FPG and body mass index (BMI) was associated with increased risk of developing pre-diabetes/T2D among adolescents, aged 10 - 19 years, with corresponding hazard ratios (HR) of 1.89 (1.6 - 2.23) and 1.43 (1.08 - 1.90), respectively (11). Also, this study showed that the paternal history of T2D was linked with increased risk for pre-diabetes/T2D in the adolescents [HR: 1.63 (1.02 - 2.60)].

3.3.2. Adults

Data from the TLGS showed that during 1999 - 2008 (median follow-up time of 6 years), risk for developing T2D was 30% higher in females than in males, after adjusting for age; however, there were no significant gender differences in risk of T2D in the multivariate adjusted model. The independent risk factors were age, family history of diabetes, BMI, abdominal obesity, high triglycerides (TG) (TG > 2.2 mmol/L), IFG, Isolated IGT, and combined IFG and IGT (15). Table 1 shows the odds ratio (OR) for above mentioned risk factors derived from the multivariate logistic regression model (15).

On the basis of survival analysis of 8,400 people (3,620 men) from TLGS and a median of 9.5 years follow-up, a significant association was observed for 2h-PG, FPG and family history of diabetes with risk for incident T2D in the total population, with a 42% increased risk per each unit increment of 2h-PG [HR: 1.42 (1.35 - 1.49)] and FPG [HR: 3.39 (2.93 - 3.91)] (13). Family history of diabetes was associated with 64% (1.40 - 1.92) increased risk of T2D in the total population. Moreover, a significant relation was found between the wrist circumference (cm) and incident T2D [HR: 1.16 (1.03 - 1.31)] among women. On the other hand, among men, BMI and low educational status (illiterate/primary school) was associated with the incidence of T2D [HR: 1.12 (1.02 - 1.22) and 1.80 (1.23 - 2.36), respectively] (Table 2) (13).

Further research conducted on the TLGS population showed the potential predictive role of some biomarkers and anthropometric measures for developing T2D. In a

Table 1. Variables Predictive of the Incident Type 2 Diabetes During 6 Years of Follow-Up, Tehran Lipid and Glucose Study[a,b]

Variables	OR (95% CI)	P Value
Age, per 10 years	1.2 (1.1 - 1.3)	0.008
Family history of diabetes	1.8 (1.3 - 2.5)	< 0.001
Body mass index ≥ 30 kg/m²	2.3 (1.5 - 3.6)	< 0.001
Abdominal obesity	1.9 (1.4 - 2.6)	0.001
High triglyceride	1.4 (1.1 - 1.9)	0.04
Glucose tolerance category		
Normal	1	-
Isolated IFG	7.4 (3.6 - 15.0)	< 0.001
Isolated IGT	5.9 (4.2 - 8.4)	< 0.001
IFG/IGT	42.2 (23.8 - 74.9)	< 0.001

Abbreviations: CI, confidence interval; FPG, fasting plasma glucose; 2h-PG, 2-h postchallenge plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OR, odds ratio; TG, triglyceride.
[a]The data adapted from "Population-based incidence of Type 2 diabetes and its associated risk factors: results from a six-year cohort study in Iran" (Harati et al.) (15).
[b]Abdominal obesity: Waist circumference greater than 88 cm for women and 102 cm for men. High triglyceride: Triglyceride > 2.2 mmol/L. Isolated IFG: FPG 5.6 - 6.9 and 2h-PG < 7.7 mmol/L. Isolated IGT: 2h-PG 7.7 to 11.0 and FPG < 5.6 mmol/L.

study with a median follow-up of 9.2 years (1999 - 2012), fasting hyperinsulinaemia was found to be a strong risk factor for progression to T2D in adults, aged ≥ 20 years with normal fasting glucose/normal glucose tolerance at baseline. The HR (95% CI) for incident T2D was 2.01 (1.03 - 3.89) and 2.04 (1.22 - 3.40) for fasting hyperinsulinaemia in men and women, respectively (16). In a nested case-control study using data from the TLGS, the relation between 25-hydroxy vitamin D [25(OH) D] and newly diagnosed T2D was examined. Cases were 191 subjects of T2D diagnosed at a median follow-up of 3.6 years. The ORs for T2D were estimated using conditional logistic regression models for tertiles of serum 25(OH) D concentrations [tertile 1: 2.82-11.02 (reference), tertile 2: 11.03 - 21.80, and tertile 3: ≥ 21.82 ng/mL]. Adjusted ORs (95% CI) of T2D were 0.47 (0.25 - 0.90) and 0.43 (0.23 - 0.82), for the second and third tertiles, respectively. Results of cubic spline regression model showed an apparent threshold of ~10 ng/mL for 25(OH) D, below which the risk of newly diagnosed T2D increased dramatically (17). Another nested case-control study on 133 subjects, free of diabetes at baseline, (68 cases and 65 controls) investigated the associations of different hepatic markers including aspartate aminotransferase (AST), alanin aminotranferase (ALT), gamma glutamyl transferase (GGT), insulin and C-reactive protein (CRP) with incident T2D (18). Odds ratios were calculated for each 1 SD increment in hepatic markers; both ALT and GGT were associated with diabetes incidence when adjusted for CRP and insulin. After Further adjustment for anthropometric, blood pressure and metabolic factors, only ALT was associated with T2D incidence [OR: 3.18 (1.02 - 9.86)]. Further analysis found no statistical difference between the area under the receiver operating characteristic curves (AUC) of the models with (AUC 0.820) and without (AUC 0.802) ALT (P = 0.4). This study showed that ALT was associated with incident T2D independent of traditional risk factors; although, its addition to the traditional risk factors did not improve the performance of model (18). In another prospective evaluation with a median follow up of 8.8 years, after controlling for multiple diabetes risk factors, a 1 SD (0.9 cm in males and 1.0 cm in females) increase in wrist circumference was associated with a 17% increase in diabetes incidence in males (P = 0.012) and a 31% increase of diabetes incidence among females (P < 0.001). After controlling for the BMI or waist circumference (WC), wrist circumference was an independent predictor of T2D only among females (19).

3.4. Interactions Between Risk Factors of T2D

Findings of the TLGS also support the concept of a certain type of interaction between risk factors of T2D using decision tree algorithms. Using data from the TLGS, Ramezankhani et al. applied the decision tree approach to identify important risk factors for T2D and exploration of interactions between those factors (20, 21). In a prospective design, they examined 15 and 20 variables for the model development in men and women, respectively, and found 2h - PG, FPG and waist-to-height ratio (WHtR) as the most important predictors for incidence of T2D in both genders (20); age was also found to be a risk factor only among men. The study was noteworthy in that it showed the interaction between those risk factors mentioned above separately for men and women. For example, among men with an FPG ≤ 4.9 mmol/L a 16% probability for incidence of T2D was seen during study period; whereas, a group of men with FPG > 5.3 mmol/L and waist to height ratio (WHtR) > 0.56 had a 84% probability for incidence of T2D. Moreover, a 12% probability for incidence of T2D was found among females who had FPG ≤ 5.2 mmol/L and WHtR ≤ 0.55, and 84% probability for incidence of T2D in a group of women with FPG > 5.2 mmol/L and WHtR > 0.56.

3.5. Cardiovascular Diseases (CVD)

In a study of 7,239 participants (3,246 men), free of CVD at baseline, T2D was associated with 70% (95% CI, 1.36 - 3.53) and more than two folds (1.74 - 2.77) increased risk of non-fatal CVD in men and women, respectively (22). In another study conducted on 8,108 participants (3,686 men), aged ≥ 30 years (23), having T2D significantly increased the risk of developing CVD (HR, 1.86 (1.57 - 2.27) during study period (1999 - 2012). Accordingly, the population attributable fraction (PAF) of diabetes was 13.87%, showing that about 14%

Table 2. Hazard Ratios of Potential Risk Factors for Incidence of Type 2 Diabetes, Tehran Lipid and Glucose Study[a]

Risk Factors	Men	P Value	Women	P Value	Total	P Value
Fasting plasma glucose, mmol/L	3.30 (2.65 - 4.10)	< 0.001	3.54 (2.94 - 4.26)	< 0.001	3.39 (2.93 - 3.91)	< 0.001
2-h postchallenge plasma glucose, mmol/L	1.43 (1.34 - 1.54)	< 0.001	1.43 (1.34 - 1.53)	< 0.001	1.42 (1.35 - 1.49)	< 0.001
Wrist circumference, cm	1.07 (0.91 - 1.26)	0.36	1.16 (1.03 - 1.31)	0.01	1.07 (1.00 - 1.16)	0.04
Family history of diabetes	1.78 (1.39 - 2.29)	< 0.001	1.54 (1.26 - 1.89)	< 0.001	1.64 (1.40 - 1.92)	< 0.001

[a]The data adapted from "Sex specific incidence rates of type 2 diabetes and its risk factors over 9 years of follow-up: Tehran lipid and glucose study" (Derakhshan et al.) (13).

of CVD was attributable to the causal effects of diabetes. Based on TLGS data from 1999 - 2010 (24), the HRs of coronary heart disease (CHD) were 3.9 (2.9 - 5.3) and 2.7 (2.0 - 3.6) in men and women with diabetes, respectively, compared to their non-diabetic peers. The PAF of diabetes was 6.7% for CHD. In another study of 5,198 participants (2,267) of TLGS (25), subjects with known diabetes mellitus (DM), but no history of CHD in either gender [HR, 1.7 (0.9 - 3.3) and 6.2 (3.6 - 10.6) in males and females, respectively)], exhibited a CHD risk comparable to non-diabetics with a history of CHD [2.1 (1.4 - 3.1) and 5.2 (3.2 - 8.3) in males and females, respectively]. Among newly diagnosed DM participants without history of CHD, the risk was comparable to nondiabetics with a prior CHD only among men [1.7 (1.1 - 2.7) vs. 2.1 (1.4 - 3.1)]. In another TLGS study conducted from 1999 to 2009 (26), T2D was associated with a 2.18-fold (95% CI, 1.34 - 3.56) increase in the risk of stroke among 2,378 participants (1,089 men), aged $\geq$ 50 years with a PAF of 22.0% for stroke.

3.6. Mortality

In a prospective analysis of 6,331 individuals, aged $\geq$ 30 years from the TLGS study with 8.6 years of follow-up (1999 - 2009), T2D was associated with increased risk of all-cause death [HR: 2.00 (1.30 - 3.09)] in the total population. The PAF of T2D for all-cause mortality was 10.1%, showing that 10.1% of mortality was attributable to the causal effects of diabetes (27). Analysis of data from the TLGS from 1999 to 2012, of 8,108 participants (4,422 women), aged $\geq$ 30 years and mean follow-up of 10.7 years, showed that T2D continues to be associated with incremental all-cause mortality [HR: 2.56 (2.08 - 3.16)]. Calculations of PAF showed that among the total population, 24.37% of mortality was attributable to the T2D (23). In a multi-state analysis of TLGS data from 1999 - 2014, conducted on 7,239 TLGS participants (3,246 men) aged $\geq$ 30 years, T2D was significantly associated with increased risk of all-cause mortality [2.72 (2.03 - 3.63) and 1.92 (1.37 - 2.67) in men and women, respectively]. A recent study of 1,198 diabetic patients, aged $\geq$ 30 years, with a median follow-up of 10 years, found that during the study period (1999 - 2012), 281 and 172 participants experienced cardiovascular diseases events and all-cause death, respectively; this study showed that FPG level of 7.22 - 10 mmol/L [HR: 1.46 (1.12 - 1.96)], FPG level $\geq$ 10 mmol/L [2.04 (1.53 - 2.72)], hypertension [1.65 (1.28 - 2.13)], hypercholesterolaemia [1.96 (1.40 - 2.75)] and high WHtR ($\geq$ 0.95 for men and $\geq$ 0.90 for women) [1.30 (0.99 - 1.70)] were significant predictors of CVD among diabetic patients. Considering all-cause mortality events, hypertension [1.70 (1.23 - 2.36)], FPG level $\geq$ 10 mmol/L [2.31 (1.55 - 3.20)] and smoking [1.45 (1.03 - 2.04)] were significant predictors (28).

3.7. Prediction of Diabetes

Several risk prediction models for incident T2D have been developed using TLGS data. A simple risk score model was developed using data from a 6-year follow-up of 3,242 TLGS participants, aged $\geq$ 20 years without diabetes at baseline (1999 - 2001). The risk score model was developed by logistic regression model (29), which included systolic blood pressure (SBP), family history of diabetes, WHtR, triglyceride-to-high-density lipoprotein cholesterol ratio (TG/HDL-C) $\geq$ 3.5 and FPG level $\geq$ 5mmol l/L. This score-based model was well calibrated (Hosmer-Lemeshow χ^2 test = 6.147, P = 0.631) and the discrimination capability, assessed by the AUC, was 0.83 (95% CI, 0.80 - 0.86); internal validity of this score-based model was assessed by the bootstrap procedure which yielded mean estimated AUC of 0.83 and non-parametrically estimated 95% CI of 0.795 - 0.855 (29). A recent TLGS study (20) developed a series of prediction models using the decision tree method to predict the incidence of T2D among an adult population of 6,647 participants (43.4% men), aged > 20 years. The study population were selected from the first (1999 - 2001) and second phases (2002 - 2005) of TLGS and were followed until 2012; two different models (with and without 2-h PG) were developed using three types of decision tree algorithms separately in men, women and total population. The entire datasets divided into two sets; 70% of the data for model development, and the remaining (30%) for the internal validation. Performance of the models was assessed using sensitivity, specificity, AUC, geometric mean (G-Mean) and the F-Measure. The Quick Unbiased Efficient Statistical Tree (QUEST) algorithm found to have the highest sensitivity (78% in both genders) and G-Mean (0.75% and 0.78% in

males and females, respectively); QUEST showed good discrimination power with AUC > 0.78 in both genders. FPG, 2h-PG, and mean arterial blood pressure (MAP) were the most important factors for incidence of T2D in both men and women. The decision tree models also identified the best cut-off point for each predictor for the best prediction of T2D among participants (20). Although both risk prediction models were internally validated by splitting methods, the external validity of these models have not yet been assessed in a different population.

3.8. Lifestyle Behaviors and Risk of T2D

In a cluster-controlled trial study, the effect of lifestyle intervention on incidence of T2D was assessed among TLGS participants (30). The lifestyle interventions were implemented through educational programs to improve dietary behaviors, increase levels of physical activity, and decrease cigarette smoking. After 3.6 years of intervention, the incidence of T2D was 12.2 and 8.2 per 1000 person-years, in the control and intervention groups, respectively, which showed 65% (95% CI; 30 - 83%) reduction in incidence of T2D in the intervention group compared to controls. Accordingly, lifestyle interventions produced greater improvement in subjects over 65 years of age and in individuals with IFG or IGT.

3.9. Life Expectancy

In a study of 7,239 participants (3,246 men), free of CVD at baseline, the effect of T2D on non-fatal CVD and all cause death, with and without non-fatal CVD, was studied using the multi-state Markov model (22). Also, a 15-year life expectancy (LE) was estimated for participants with and without diabetes; the study found that having T2D significantly increased the risks of developing non-fatal CVD [HR: 1.70 (1.36 - 3.53) and 2.19 (1.74 - 2.77) in males and females, respectively] and of all-cause mortality [2.72 (2.03 - 3.63) and 1.92 (1.37 - 2.67) in males and females, respectively]. After incident non-fatal CVD, the association between diabetes and all-cause death was not significant among women; however, the study found a greater risk of mortality among diabetic men [HR: 2.19 (1.36 - 3.53)]. The 15-year LE, free of non-fatal CVD was 1.7 and 1.4 years longer in non-diabetic men and women, respectively, than their diabetic counterparts ($P < 0.001$). Also, compared with diabetic men and women, their non-diabetic counterparts survived 1.4 and 0.7 years longer, respectively. After a non-fatal CVD, diabetes was associated with 1.3 years decrease in 15-year LE among men (22).

4. Conclusions

This paper summarizes many of the key findings related to T2D including prevalence, incidence, risk factor, and risk prediction models in the TLGS cohorts. We believe valuable information can be gained from these findings bringing us one step closer to developing prioritized programs for prevention and management of diabetes. We should emphasize the fact that in all studies included in this review, diagnosis of diabetes was based on the FPG and 2h-PG, not on the history of self-reported diabetes. Therefore, the accuracy of the results is reasonably high in the TLGS population.

In Iran, there are other cohort studies with similar data (31-34). It is only logical that aggregated data from these studies would yield a large representative database to examine risk factors and develop risk models that are applicable to most, if not all, of the Iran; this is currently underway through the "Iran Cohort Consortium" established in 2016 (35).

Although various aspects of diabetes have been investigated in TLGS, there still remains a number of issues which should be resolved in future researches, one of which is population awareness; it is unclear what proportions of the diabetic populations in TLGS were aware of their condition and what was the increase in awareness during the study period? Another important concern that should be considered in future researches is investigation of the frequency of hospitalizations among diabetic patients of the TLGS study. Also, extensive research is needed to identify how durations of pre-diabetes T2D influence clinical outcomes in TLGS participants. Current evidence suggests that increasing duration of T2D is associated with increasing CVD risk. It has been reported that the relative risk of coronary heart disease (CHD) is 1.38 times higher and the risk for CHD mortality is 1.86 times higher for each 10-year increase in duration of T2D (36). Although extensive observational researches have been conducted in the last decades on TLGS participants, research on genetic causes of T2D is in its infancy (37), which offers a good opportunity to expand our knowledge in relation with T2D in the near future. Lastly, simultaneously with ageing, that affects metabolism, nutrient intake, physical activity, and risk of chronic diseases, it will be critically important to study economical cost of treating T2D and its complications among study populations. We believe that there is a strong need to shift our studies toward randomized controlled trials to provide clinical evidence of the efficacy of the pharmacological treatment of T2D in Iranian populations.

The ultimate aim is that the improved understanding of the mechanisms of T2D and the associated risk factors will permit improved healthcare programs and implementation of new and potentially more efficient preventive strategies, which is critically important for our country with 1% annual incidence rate of T2D.

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