

# Clustering of coronary artery disease risk factors in patients with type 2 diabetes and impaired glucose tolerance

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تجمع عوامل اختطار مرض الشريان الإكليلي في السكريين من النمط 2 وخلل تحمل الغلوكوز  
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**الخلاصة:** أجرى الباحثون دراسة مستعرضة في أصفهان، جمهورية إيران الإسلامية، للمقارنة بين تكرار عوامل اختطار مرض القلب الإكليلي لدى السكريين ممن شُخص لديهم المرض حديثاً، وبين أفراد لديهم خلل تحمل الغلوكوز من جهة وبين أشخاص أسوياء من جهة أخرى. وقد بلغ معدّل انتشار الحالات المعروفة بإصابتها بالسكري 4.3% والحالات الجديدة منه 1.1% وحالات خلل تحمل الغلوكوز 6.2% لدى 3940 فرداً. فيما كان تكرار خلل شحميات الدم مختلفاً بدرجة يُعتدّ بها إحصائياً عند مقارنة السكريين بالأفراد الأسوياء. كما كان هناك معدّل انتشار أعلى لعوامل الاختطار لدى النساء (ازدياد مُنسب كتلة الجسم أو محيط الخصر المترافق بخلل شحميات الدم). وتوضح الدراسة أهمية الاستراتيجيات المحددة للوقاية من السكري وتشخيصه المبكر في المجتمع.

**ABSTRACT** A cross-sectional study in Isfahan city, Islamic Republic of Iran, compared the frequency of coronary artery disease risk factors in known and newly diagnosed diabetic patients and individuals with impaired glucose tolerance (IGT) with normal individuals. The prevalence of known cases of diabetes, new cases of diabetes and cases with IGT in the general population sample of 3940 were 4.3%, 1.1%, and 6.2% respectively. The frequency of dyslipidaemia was significantly different comparing diabetics and normal individuals. There was a significantly higher prevalence of risk factors (i.e. increased body mass index or waist circumference accompanied by dyslipidaemia) in the female population. The study highlights the importance of defining strategies for prevention and early diagnosis of diabetes in the community.

## Concentration des facteurs de risque de coronaropathie chez des patients souffrant de diabète de type 2 et d'intolérance au glucose

**RÉSUMÉ** Une étude transversale réalisée dans la ville d'Ispahan (République islamique d'Iran) a comparé la fréquence des facteurs de risque de coronaropathie chez des patients diabétiques connus et nouvellement diagnostiqués et des sujets présentant une intolérance au glucose avec celle observée chez des sujets normaux. La prévalence des cas connus de diabète, des nouveaux cas de diabète et des cas d'intolérance au glucose parmi les 3940 personnes de l'échantillon de la population générale était respectivement de 4,3 %, 1,1 % et 6,2 %. La fréquence de la dyslipidémie était significativement différente entre les diabétiques et les sujets normaux. Il existait une prévalence significativement plus élevée des facteurs de risque (à savoir l'augmentation de l'indice de masse corporelle ou du tour de taille, accompagnée de dyslipidémie) dans la population féminine. L'étude souligne qu'il est important de définir des stratégies de prévention et de diagnostic précoce au niveau de la population.

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## Introduction

Diabetes is a leading cause of mortality worldwide. Nearly 154 million lives in the world are affected by diabetes [1]. The cost of treatment and care of diabetic patients in the United States amounts to some US\$ 98 million annually [2]. The prevalence of diabetes in developing countries is on the rise; for example, in the Islamic Republic of Iran estimates provided by epidemiological studies have put the prevalence of diabetes in the population aged over 30 years at about 10.6% [3].

A multitude of underlying factors are involved in the aetiology of type 2 diabetes. Impaired glucose tolerance (IGT) and obesity are among the most important diabetes risk factors [4].

Epidemiological studies, including the Framingham studies, show that the risk of coronary artery disease (CAD) and myocardial infarction increase 1.2–4 times in diabetic patients [5]. Increased prevalence of CAD in diabetic patients is accompanied by impairment of the metabolism of lipids and lipoproteins [5]. Diabetes is a cardiovascular risk factor associated with arterial hypertension and accelerated atherosclerosis [6]. Results of the Framingham studies and the World Health Organization ERICA research group have clearly demonstrated the importance of clusters of risk factors [7].

The prevalence of diabetes is increasing in the Islamic Republic of Iran. During recent years, nationwide programmes have been launched for primary and secondary prevention through patient identification and tertiary prevention of complications. Failure to detect and appropriately control the disease will increase future complications. The present study was conducted with the objective of comparing the frequency of some of the CAD risk factors in diabetic pa-

tients and individuals with IGT with normal individuals and to compare the frequency of these risk factors in known and new cases of diabetes.

## Methods

This is a descriptive, cross-sectional study based on data obtained from the first phase of the Isfahan Healthy Heart Program in 2000–01. The methodology has been fully described elsewhere [8].

### Sample

The baseline survey of 3940 randomly selected adults aged  $\geq 19$  years was conducted with a 2-stage cluster sample in the city of Isfahan, the 2nd largest city in the Islamic Republic of Iran. Criteria for inclusion in the study were: being older than 19 years, having Iranian nationality, having lived in Isfahan for a minimum of 6 months, being mentally competent and, for females, not being pregnant. Individuals who did not meet one or more of these criteria were excluded from the study. Given the relatively equal distribution of sexes in the Islamic Republic of Iran, equal numbers of men and women were selected for the study.

### Data collection

Informed consent was obtained from the participants and questionnaires of approved validity (as verified in the experimental phase of the study) were used to collect the data [8].

Using portable scales (Secca®, Germany), trained staff measured the heights and weights of participants who were lightly dressed and without shoes. Waist circumference (WC) was measured at a level midway between the lower rib margin and iliac crest to the nearest half centimetre. The cut-off point for abdominal obesity was  $WC \geq$

102 cm for men and  $\geq 88$  cm for women. Body mass index (BMI) was calculated as weight divided by height squared ( $\text{kg/m}^2$ ). Overweight was defined as BMI 25–29.9  $\text{kg/m}^2$ , and obesity as BMI  $\geq 30$   $\text{kg/m}^2$  for all subjects [9].

The blood pressure of participants was measured with mercury-based sphygmomanometers by trained physicians using standard WHO criteria. Blood pressure was measured twice on the right after 5 minutes of rest. The average of the 2 measurements was recorded as the individual's blood pressure. According to the WHO definition, individuals with systolic blood pressure  $\geq 140$  mmHg or those with diastolic blood pressure  $\geq 90$  mmHg were considered hypertensive [10].

Blood samples were taken from the participants after 14 hours fasting. Biochemical parameters, including total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) were measured. TC and TG were measured with a German Eppendorf Elan 2000 auto-analyser using the enzymatic method. A similar enzymatic method was applied to measure HDL-C using the heparin–manganese deposition technique [11]. LDL-C was measured in specimens with TG  $\leq 400$  mg/dL using the Friedewald formula [12]. In other instances, LDL-C was measured using special kits. Patients with one or more of the following conditions were considered as having dyslipidaemia [10]: TG  $\geq 200$  mg/dL, TC  $\geq 240$  mg/dL, HDL-C  $< 40$  mg/dL, LDL-C  $> 100$  mg/dL.

Sodium fluoride was used to separate plasma from the blood specimens before measuring blood glucose via the enzymatic glucose oxidase method. Individuals whose fasting blood sugar levels were  $\geq 126$  mg/dL or those receiving glucose lowering medications were considered as diabetic

[13]. Known cases of diabetes were individuals for whom the diagnosis of diabetes had been established by a physician in the past, or those who were under treatment with antidiabetic drugs. Individuals whose 2-hour postprandial blood glucose (2 hours after taking glucose orally) was 140–200 mg/dL were considered to have IGT.

All of the tests were conducted at Isfahan Cardiovascular Research Centre laboratory which uses the criteria of the Iranian Ministry of Health and Medical Education and is under the quality control of the University of St Rafael, Belgium.

### Data analysis

The frequency of each of the CAD risk factors, including hypertension, increased WC, increased BMI and various types of dyslipidaemia was compared independently of other risk factors and compared between the diabetes groups under study, i.e. known cases of diabetes, new cases of diabetes, individuals with IGT and normal individuals. The risk factors were separately added to each other and compared in the groups under study. Chi-squared and Fisher exact tests were used to compare the frequency distribution of different risk factors between the 2 sexes and between the diabetes groups using the Windows-based software SPSS, version 11.

### Results

A total of 3940 people (2026 women and 1914 men) were studied. The women and men studied had a mean age of 38.7 (SD 0.31) years and 39.0 (SD 0.35) years, respectively.

Mean fasting blood glucose and 2-hour postprandial glucose were 85.4 (SD 0.57) mg/dL and 104.9 (SD 0.91) mg/dL respectively. Mean BMI and WC were 26.2 (SD 0.09)  $\text{kg/m}^2$  and 94.1 (SD 0.2) cm.

The prevalence of known cases of diabetes, new cases of diabetes and cases of IGT were 4.3%, 1.1%, and 6.2% respectively in the study population; the values were 3.7%, 1.0% and 5.3% respectively in men, and 4.9%, 1.2% and 7.1% respectively in women.

Comparison of single risk factors, and combinations of risk factors, in known cases of diabetes, new cases of diabetes and cases of IGT yielded significant differences from those in healthy individuals ( $P \leq 0.05$ ) (Table 1). Comparison of the frequency of all types of dyslipidaemia and hypertension

showed a significant difference in known cases of diabetes, new cases and IGT. Comparison of the frequency of dyslipidaemia and increased WC in cases of IGT also showed a significant difference ( $P \leq 0.05$ ).

Table 2 presents the prevalence of CAD risk factors in isolation or in association with other risk factors in known and new cases of diabetes according to sex. Only increased BMI in association with dyslipidaemia in the total study population showed a significant difference between groups ( $P \leq 0.05$ ).

**Table 1 Comparison of the frequency of cardiovascular disease risk factors between known cases and new cases of diabetes, and cases of impaired glucose tolerance (IGT) with normal individuals**

Variable	Normal (n = 3489)		Diabetics				IGT (n = 246)	
	No.	%	Known (n = 175)		New (n = 40)		No.	%
Hypertension <sup>a</sup>	15	0.4	1	0.6	0	0.0	1	0.4
Overweight <sup>b</sup>	137	3.9	3	1.7	0	0.0	5	2.0
Obesity <sup>c</sup>	64	1.8	1	0.6	1	2.5	2	0.8
Increased WC <sup>d</sup>	191	5.4	4	2.3**	1	2.5**	6	2.4**
Dyslipidaemia <sup>e</sup>	871	24.9	13	7.4*	0	0.0	18	7.3*
Hypertension + increased BMI	29	0.8	0	0.0	1	2.5**	2	0.8
Hypertension + increased WC	26	0.7	0	0.0	0	0.0	1	0.4
Hypertension + dyslipidaemia	91	2.6	10	5.7*	2	5.0**	12	4.9**
Increased BMI + dyslipidaemia	1361	39.0	59	33.7	22	55.0**	123	50.0**
Increased WC + dyslipidaemia	1092	31.2	52	29.7	18	45.0	105	42.7**
Hypertension + increased BMI + dyslipidaemia	376	10.7	65	37.1**	14	35.0**	66	26.8**
Hypertension + increased WC + dyslipidaemia	341	9.7	65	37.1**	13	32.5**	61	24.8**

<sup>a</sup>Systolic blood pressure  $\geq 140$  mm/Hg or diastolic blood pressure  $\geq 90$  mm/Hg, or receiving antihypertensive medication.

<sup>b</sup> $25 \text{ kg/m}^2 \leq \text{BMI} < 30 \text{ kg/m}^2$ .

<sup>c</sup> $\text{BMI} \geq 30 \text{ kg/m}^2$ .

<sup>d</sup> $> 88$  cm in women,  $> 102$  cm in men.

<sup>e</sup>Triglycerides  $\geq 200$  mg/dL or high-density lipoprotein cholesterol  $< 40$  mg/dL, or total cholesterol  $\geq 240$  mg/dL, and low-density lipoprotein cholesterol  $> 100$  mg/dL.

\* $P \leq 0.05$ ; \*\* $P \leq 0.001$ .

n = number of participants; WC = waist circumference; BMI = body mass index.

**Table 2 Comparison of the frequency of cardiovascular disease risk factors between known cases of diabetes and new cases of diabetes, according to sex**

Variable	Men			Women			Total		
	Known diabetics (n = 75) No. %	New diabetics (n = 14) No. %	Known diabetics (n = 100) No. %	New diabetics (n = 26) No. %	Known diabetics (n = 175) No. %	New diabetics (n = 40) No. %			
Hypertension <sup>a</sup>	1 1.3	0 0.0	0 0.0	0 0.0	1 0.6	0 0.0			
Overweight <sup>b</sup>	0 0.0	0 0.0	3 3.0	0 0.0	3 1.7	0 0.0			
Obesity <sup>c</sup>	1 1.3	0 0.0	0 0.0	1 3.8	1 0.6	1 2.5			
Increased WC <sup>d</sup>	1 1.3	0 0.0	3 3.0	1 3.8	4 2.2	1 2.5			
Dyslipidaemia <sup>e</sup>	12 16.0	0 0.0	1 1.0	0 0.0	13 7.4	0 0.0			
Hypertension + increased BMI	0 0.0	1 7.1	0 0.0	0 0.0	0 0.0	1 2.5			
Hypertension + increased WC	0 0.0	0 0.0	0 0.0	0 0.0	0 0.0	0 0.0			
Hypertension + dyslipidaemia	10 13.3	1 7.1	0 0.0	1 3.8	10 5.5	2 5.0			
Increased BMI + dyslipidaemia	25 33.3	10 71.4	34 34.0	12 46.2	59 33.7*	22 55.0			
Increased WC + dyslipidaemia	9 12.0	6 42.9	43 43.0	12 46.2	52 29.1	18 45.0			
Hypertension + increased BMI + dyslipidaemia	20 26.7	8 57.1	45 45.0	6 23.1	65 37.1	14 35.0			
Hypertension + increased WC + dyslipidaemia	13 17.3	6 42.9	52 52.0	7 26.9	65 37.1	13 32.5			

<sup>a</sup>Systolic blood pressure  $\geq 140$  mm/Hg or diastolic blood pressure  $\geq 90$  mm/Hg, or receiving antihypertensive medication.

<sup>b</sup> $25 \text{ kg/m}^2 \leq \text{BMI} < 30 \text{ kg/m}^2$ .

<sup>c</sup> $\text{BMI} \geq 30 \text{ kg/m}^2$ .

<sup>d</sup> $> 88$  cm in women,  $> 102$  cm in men.

<sup>e</sup>Triglycerides  $\geq 200$  mg/dL or high-density lipoprotein cholesterol  $< 40$  mg/dL, or total cholesterol  $\geq 240$  mg/dL, and low-density lipoprotein cholesterol  $> 100$  mg/dL.

\* $P \leq 0.05$ .

n = number of participants; WC = waist circumference; BMI = body mass index.

Table 3 compares the frequency of CAD risk factors between men and women in known cases of diabetes, new cases of diabetes and cases of IGT. The prevalence of dyslipidaemia per se according to sex was significant ( $P \leq 0.05$ ).

Comparison of the frequency of all types of dyslipidaemia and hypertension showed a significant difference in known cases of diabetes. Comparison of the frequency of dyslipidaemia and increased WC in known cases of diabetes and cases of IGT also showed a significant difference ( $P \leq 0.05$ ). Only in previously diagnosed cases of diabetes did we observe a significant difference when comparing all CAD risk factors between men and women ( $P \leq 0.05$ ).

## Discussion

In the present study, the prevalence of new cases of diabetes was considerably lower than known cases of diabetes. However, new and known cases of diabetes were found to be equally prevalent in studies conducted in countries such as the United States, Sudan, Iraq and Kuwait [14,15]. Identification of new cases of diabetes can contribute effectively to treatment and prevention of its macro- and microvascular complications by prompting timely control of blood glucose [16].

The results of one study in the Islamic Republic of Iran showed that diabetes is more prevalent in women than men; this can be accounted for by women's greater propensity towards developing diabetes, which is partly due to a more sedentary lifestyle, obesity and inappropriate nutrition [17]. In our study the prevalence of diabetes was 6.1% and 4.7% in women and men, respectively.

In our study the prevalence of IGT was 6.2% in the general population. One study

of Pima Indians showed that nearly one-third of individuals with IGT were at risk of diabetes [18]. Several factors are involved in escalation of the risk of atherosclerosis in diabetics. These include increased blood glucose levels and insulin resistance. The latter can be considered as a cluster of risk factors that contribute individually or collectively to atherosclerosis in the study population [19].

In this study, only when the prevalence of CAD risk factors was compared between the 2 groups we did observe a significant difference for 2 of the risk factors, namely increased WC in women and dyslipidaemia in both sexes. Central obesity is considered a risk factor in diabetes [20]. The results of other studies showed that central obesity was a better predictor of CAD and diabetes than BMI [21].

The results of studies on American Indians did not show any relationship between hypertension and increased fasting insulin when increased blood glucose and dyslipidaemia were not concomitantly present. The relationship was strongest when dyslipidaemia was considered as a risk factor in hyperglycaemic individuals [22]. Dyslipidaemia poses a major risk to the lives of hyperglycaemic individuals [23]. In the present study, a significant difference was observed between patients and healthy individuals when the cumulative frequency of a number of risk factors was compared between the 2 groups. Not only in diabetics but also in cases of IGT, this difference could even be observed in patients suffering from hypertension and dyslipidaemia. Studies by Zimmet et al. showed a strong relationship between increased insulin resistance and IGT [24]. Notably, a significant difference was observed between healthy individuals and patients, when lipid disorders were accompanied by other risk factors.

**Table 3 Comparison of the frequency of cardiovascular disease risk factors between men and women in known cases of diabetes, new cases of diabetes and cases of impaired glucose tolerance (IGT)**

Variable	Known diabetics		New diabetics		IGT	
	Men (n = 75) No. %	Women (n = 100) No. %	Men (n = 14) No. %	Women (n = 26) No. %	Men (n = 102) No. %	Women (n = 144) No. %
Hypertension <sup>a</sup>	1 1.3	0 0.0	0 0.0	0 0.0	0 0.0	1 0.7
Overweight <sup>b</sup>	0 0.0	3 3.0	0 0.0	0 0.0	1 1.0	4 2.8
Obesity <sup>c</sup>	1 1.3	0 0.0	0 0.0	1 3.8	0 0.0	2 1.4
Increased WC <sup>d</sup>	1 1.3	3 3.0	0 0.0	1 3.8	0 0.0	6 4.2
Dyslipidaemia <sup>e</sup>	12 16.0**	1 1.0	0 0.0	0 0.0	15 14.7**	3 2.1
Hypertension + increased BMI	0 0.0	0 0.0	1 7.1	0 0.0	1 1.0	1 0.7
Hypertension + increased WC	0 0.0	0 0.0	0 0.0	0 0.0	0 0.0	1 0.7
Hypertension + dyslipidaemia	10 13.3**	0 0.0	1 7.1	1 3.8	8 7.8	4 2.8
Increased BMI + dyslipidaemia	25 33.3	34 34.0	10 71.4	12 46.2	41 40.2	73 50.7
Increased WC + dyslipidaemia	9 12.0**	43 43.0	6 42.9	12 46.2	23 22.5**	82 56.9
Hypertension + increased BMI + dyslipidaemia	20 26.7*	45 45.0	8 57.1	6 23.1	29 28.4	37 25.7
Hypertension + increased WC + dyslipidaemia	13 17.3**	52 52.0	6 42.9	7 26.9	19 18.6	42 29.2

<sup>a</sup>Systolic blood pressure  $\geq 140$  mm/Hg or diastolic blood pressure  $\geq 90$  mmHg, or receiving antihypertensive medication.

<sup>b</sup>25 kg/m<sup>2</sup>  $\leq$  BMI < 30 kg/m<sup>2</sup>.

<sup>c</sup>BMI  $\geq 30$  kg/m<sup>2</sup>.

<sup>d</sup> > 88 cm in women, > 102 cm in men.

<sup>e</sup>Triglycerides  $\geq 200$  mg/dL or high-density lipoprotein cholesterol < 40 mg/dL, or total cholesterol  $\geq 240$  mg/dL, and low-density lipoprotein cholesterol > 100 mg/dL.

\*P  $\leq 0.05$ ; \*\*P  $\leq 0.001$ .

n = number of participants; WC = waist circumference; BMI = body mass index.

This relation grows stronger when a number of risk factors are considered collectively [24]. Not only are these risk factors additive, but they also display a synergistic effect [25]. Except when increased BMI and dyslipidaemia occurred concomitantly, comparison of the frequency of risk factors between newly diagnosed and known cases of diabetes did not yield a significant result. Various studies have shown the high prevalence of CAD risk factors in all diabetic patients, even those newly diagnosed with diabetes [22]. They are indicative of the speedy progression of vascular lesions in diabetic patients and highlight the need for a persistent screening system for identification, control and treatment of diabetic patients. CAD risk factors are present even in patients who are in the initial stages of developing glucose intolerance [26].

Collective comparison of risk factors between healthy individuals and those with IGT showed a significant difference in this study. A number of studies showed that patients with insight into their disease and those aware of having risk factors have a greater incentive to modify their lifestyle [27–29]. Comparison of the frequency of dyslipidaemia in men and women showed that dyslipidaemia *per se* can be regarded as a risk factor in hyperglycaemic individuals, especially men. It has been shown that dyslipidaemia is an important risk factor in the development of atherosclerosis in diabetic patients [28]. This condition is more prominent in men [29], which may be due to a faster increase in TC and LDL-C in men or higher levels of HDL-C in women, since HDL-C protects against an increase in TG or LDL-C levels [30].

In the present study, when the frequency of dyslipidaemia was compared between

men and women in conjunction with the increase in obesity indices (i.e. WC, BMI), the prevalence of these risk factors was higher in women. This difference was significant in known cases of diabetes. On the other hand, increased WC is accompanied by lipid profile disorders which in turn are directly related to the risk of type 2 diabetes [31]. As stated earlier, diabetes is more prevalent in women than in men. The results of several studies, including the National Health and Nutrition Examination Survey (NHANES) showed that overweight and obesity were more prevalent in women than in men, both in diabetics and in individuals with IGT [32].

The results of the present study are indicative of the high prevalence of risk factors, especially obesity and dyslipidaemia in the population of diabetic patients in Isfahan. The frequency of risk factors was high in all groups of diabetics, even in new cases of the disease and those who are in the pre-diabetic stage, i.e. IGT, there is a strong relationship between CAD risk factors and type 2 diabetes. Diabetic patients are at a higher risk of CAD compared to the normal population.

In similar studies conducted on the urban population of Tehran to determine the prevalence of cardiovascular risk factors, the prevalence of dyslipidaemia in normal individuals was found to be greater in newly detected diabetic patients. The same studies showed that dyslipidaemia was accompanied by increased BMI and [33] abdominal obesity [21].

We recommend that strategies for prevention and diagnosis of diabetes must be defined in accordance with the magnitude of risk factors in the community.

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