Body weight changes and diabetes mellitus incident: A cohort study from the Middle East

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Keywords

Summary

Objective. *Obesity is a known risk factor for diabetes, but the effect of weight changes on the incidence of diabetes is not yet determined. This study aims to evaluate the long-term effects of weight change [based on body mass index (BMI)] on the incidence of diabetes mellitus (DM) in a middle eastern population.*
Method. *In the Isfahan Cohort Study (ICS) 6504 adults equal or greater than 35 years of age were recruited at 2001 and were followed until 2013. Absolute BMI changes (ΔBMI) were calculated by subtracting the baseline BMI from the BMI measured at follow-ups. To compare participants with different baseline BMI easier, relative changes in BMI were quantified as the percentage of changes from baseline. DM was assessed based on standard definitions. Multivariable Cox regression was used to determine the association between ΔBMI and the incidence of diabetes.*

Results. *During follow-ups, 261 new cases of diabetes were recorded, with an IR of 3401.29 per 100,000 P-Y. The highest number of new cases of type 2 DM belongs to participants with overweight and obesity who had minimal BMI changes (less than 5% of their baseline BMI limits; 42 and 38 new cases, respectively). Participants who were obese at baseline and had lost more than 10% or gained 5-10% of baseline BMI were in the groups with the highest IR [360.05 - 95% CI (239.3-541.8) and 322.39 - 95% CI (178.5-582.1) respectively]. There was no significant association between BMI changes and the incidence of DM in the participants with normal BMI, overweight, and obesity at baseline in cure and adjusted models.*
Conclusions. *This study showed there was no significant association between diabetes mellitus incidence and BMI changes.*

Introduction

Diabetes mellitus (DM) is a chronic disease characterized by increased blood glucose concentration and is known as a major risk factor for cardiovascular diseases (CVD) and a higher risk of mortality and morbidity [1, 2]. The prevalence of DM is rapidly increasing over the world, such that the number of diabetic patients has doubled over the last 30 years [3], estimates show that the prevalence of diabetes and mortality and morbidities associated with diabetes will continue to increase across the globe [1]. Genetics and acquired risk factors with insulin resistance pathology play an important role in the pathogenesis of DM. Obesity is one of the acquired factors that are widespread in the world today and has a specific role in the incidence of diabetes [4]. In the Middle Easter obesity has one of the highest ranks in the world, a review study done in 2011 shows the prevalence of overweight and obesity to be 50-80% among adults in the Middle East [5]. Another study covering 52 countries worldwide shows adults in the Middle East

have the highest mean BMI after the USA [6]. BMI is a measurement derived from the mass (weight) and height related to the extent of obesity. In the field of obesity and diabetes, some studies show BMI > 30 kg/m^2 compared to normal BMI (BMI < 25 kg/m^2) is associated with a 3-10 times greater risk of developing diabetes [7]. Other than BMI measured at a single time point, the BMI increase (weight gain) has shown to be a risk factor for diabetes [8].
A Scientometrics study in the Middle East shows between 1990-2013 number of obesity/overweight studies has had an increasing trend [9]. Although the association between obesity and the prevalence of diabetes is definite, studies on long-term BMI changes and the incidence of diabetes are limited and inconsistent. Some studies have shown moderate weight loss (7-10%) results in a significant reduction of incidence of diabetes (> 40%) among high-risk groups [10-15]. Some studies suggest almost any amount of weight gain is associated with an increased risk of incident diabetes [16, 17]. Other observational studies show inconclusive or contradictory results about

the association between long-term BMI change and the risk of DM [18-21]. Accordingly, this epidemiologic survey aims to evaluate the effect of long-term BMI changes on the incidence of diabetes in the Isfahan Cohort Study, a cohort in the Middle East region.

Method

STUDY POPULATION

The Isfahan Cohort Study (ICS) is a population-based study with a representative population of 6504 adults equal to or older than 35 years of age, living in urban and rural areas of three counties (Isfahan, Arak, and Najaf Abad) in central Iran [22]. Subjects were participants in the baseline survey of the Isfahan Healthy Heart Program (IHHP), a community trial for CVD. Recruitment started from January 2nd to September 28th, 2001, and subjects were followed for 13 years. Participants were selected by multistage random sampling for subject enrolment to reflect age, sex, and urban/rural distribution of the community [23]. After recruiting, subjects were followed in 2005-2006 and 2010-2011. The interview and attendance to clinical examination response rates were 98% and 95% respectively. For this study, participants without a history of DM at baseline who were present until the fifth follow-up (2013) were included. The study's ethical approval was contained by the Ethical Committee of Isfahan Cardiovascular Research Center, a WHO collaborating center.

BMI MEASUREMENT

Height and weight measurements were conducted by a secured metal ruler barefoot and a calibrated scale in light clothing. BMI was calculated as weight (kg) divided by height squared (m^2). Participants were divided into three groups "under or normal weight" (MBI < 24.9 kg/m^2), "overweight" (BMI: 25-29.9 kg/m^2), and "obese" (BMI > 30 kg/m^2) as Health Canada's Guideline for Body Weight Classification [23]. Absolute changes in BMI (ΔBMI) were calculated by subtracting the baseline BMI from the BMI measured at follow-ups. To compare participants with different baseline BMI easier, relative changes in BMI were quantified as the percentage of changes from baseline. The magnitude of ΔBMI was further classified into "minimal" ($\pm$5%), "moderate" ($\pm$5-10%), and "large" (> $\pm$10%).

DIABETIC CASE DEFINITION

Subjects with fasting plasma glucose (FPG) greater than 126 mg/dl (7.0 mmol/L) or a 2-hour post-challenge glucose value of more than 200 mg/dl (11.1 mmol/L) or being on anti-diabetes medication were defined to have diabetes [24].

OTHER VARIABLES

Based on risk factors recorded for DM [25], variables are further assessed in this study. Collecting data was carried out using questionnaires by trained health professionals [26]. The quality of diet was assessed based on a validated 48-item food frequency questionnaire (FFQ) [27]. Participants have reported the frequency of consumption of any of the food items, on a daily, weekly, and monthly basis. Data on physical activity was obtained based on 4 activity domains of job-related activity; transportation-related activity; housework and house-maintenance activity; and sports and leisure time activity. Information about the frequency, time spent, and intensity of these activities was gathered [28]. Smoking status and parental DM history also were assessed.

STATISTICAL ANALYSIS

Data are reported as mean ± SD for continuous and number (percent) for categorical variables. Kolmogorov-Smirnov test was used for testing the normality assumption. ANOVA with post-hoc test and chi-square test was used for comparing mean and frequency between groups respectively. The percentage of changes was calculated as the difference between two values divided by baseline multiple 100. The incidence rate is a measure of the frequency with which diabetes occurs over 13 years of follow-up when the denominator is the product of the person-time of the at-risk population. Crude and adjusted Cox regression models were used to evaluate the relationship between occurring diabetes and risk factors. Also, a hazard ratio with a 95% CI interval was reported. StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP. was used for analyzing data. A p-value less than 0.05 are considered significant.

Results

In this population-based study, 771 women and 786 men (a total of 1,557 participants) with a mean age of 47.11 were included. Table I reports the demographic health and lifestyle factors of study participants at baseline according to BMI categories. As shown in Table I, the mean age in all groups is almost the same. Over 77% of female and 56% of male participants are either overweight or obese which makes a total of 74.5% of all participants not being in the normal range. To compare overweight and obese participants, individuals with normal BMI are more physically active and have a healthier diet. The majorities of smokers (current or former smokers) have normal BMI and are overweight and then obese participants are less likely to have a smoking history.

In follow-up period, both women and men with normal BMI had the greatest mean changes (13.37 ± 17.72% and 7.17 ± 12.35% weight gain respectively). On average, participants in normal and overweight groups experienced weight gain and obese individuals experienced weight loss (0.84 ± 11.11% for women and 2.72 ± 12.29% for men). The majority of participants (both men and women) had minimal BMI changes (± 5% of their baseline BMI limits) after follow-up (38.0% women, 40.2% men). Besides minimal changes, those

Tab. I. Demographic health and lifestyle factors by baseline body mass index (BMI) categories.

Variables	Normal/underweight < 25 kg/m² n = 513	Overweight 25-29.9 kg/m² n = 648	Obese ≥ 30 kg/m² n = 396
Age (year) Mean (SD)	47.33 (9.8)	47.37 (9.57)	46.39 (8.19)
Sex Mean (%)			
Male	340 (66.3%)	334 (51.5%)	112 (28.3%)
Female	173 (33.7%)	314 (48.5%)	284 (71.7%)
Smoking status Mean (%)			
Current smoker	137 (26.8%)	88 (13.6%)	39 (9.8%)
Former smoker	34 (6.6%)	38 (5.9%)	12 (3.0%)
Never	341 (66.6%)	521 (80.5%)	345 (87.1%)
Physically active Mean (SD)	1018.85 (595.61)	941.66 (555.55)	828.16 (522.08)
Healthy eating index Mean (SD)	0.99 (0.26)	0.94 (0.26)	0.89 (0.29)
Parental history of diabetes (%)	28.1%	37.6%	34.3%

who have gained more than 10% of their baseline BMI (24.3% women, 23.0% men) and then who have gained 5-10% of baseline BMI (17.8% woman, 16.4% men) are the majority of the study population. Only 11.2% of women and 9.2% of men lost more than 10% of baseline BMI, and 8.8% of women and 11.2% of men lost 5-10% of their baseline BMI (Tab. II).

After 13 years of follow-up, a total of 261 new cases of DM were identified out of 9926.7 per year (P-Y), with an incidence rate (IR) of 3401.29 per 100,000 P-Y. Table III shows the highest number of new cases of type 2 DM belongs to participants with overweight and obesity who had minimal BMI changes (less than 5% of their baseline BMI limits; 42 and 38 new cases, respectively). Participants with normal BMI who had lost 5-10% and more than 10% of their baseline BMI had the lowest number of new cases of DM. Participants who were obese at baseline and had lost more than 10% or gained 5-10% of baseline BMI were in the groups with the highest IR [360.05 - 95% CI (239.3-541.8) and 322.39 - 95% CI (178.5-582.1) respectively]. The lowest IR belongs to participants who had normal BMI at baseline and 5-10% loss [97.01-95% CI (24.3-387.9)]. Since the

majority of the population study had minimal changes (1030.1, 1816.9, 1028.7 P-Y in normal, overweight, and obese groups respectively) it might explain the higher number of new DM cases in the mentioned groups. It would appear from the high IR in the obesity group and the low IR in the group with normal BMI at baseline, that baseline BMI has had a great role on the incidence of DM (Tab. III).

When estimating the association of BMI changes and the incidence of DM in the total study population, participants with normal BMI, overweight, and obesity at baseline, had no significant relation either with no adjustments, adjustment with age and sex and adjustment with age, sex, parental history of diabetes, smoking status, healthy eating index, and physical activity (Tab. IV).

Discussion

In this study, no significant relations between weight changes and incidence of DM in all categories of normal BMI, overweight, and obese of the Isfahan Cohort Study population were seen. The mean age for each

Tab. II. Body mass index (BMI) change from the baseline (ΔBMI).

ΔBMI	Baseline BMI and 2013 survey			
	Women N = 771		Men N = 786	
ΔBMI (absolute, kg/m²) by baseline BMI category				
Normal/underweight	-2.82 ± 3.69		-1.55 ± 2.64	
Overweight	-1.07 ± 3.26		-0.42 ± 2.72	
Obese	0.33 ± 3.73		0.92 ± 4.06	
ΔBMI (relative, %) by baseline BMI category				
Normal/underweight	-13.37 ± 17.72		-7.17 ± 12.35	
Overweight	-3.97 ± 12.25		-1.61 ± 10.10	
Obese	0.84 ± 11.11		2.72 ± 12.29	
Relative ΔBMI category	Proportion (%)	Baseline BMI (kg/m²)	Proportion (%)	Baseline BMI (kg/m²)
> 10% loss	11.2%	31.21 ± 4.65	9.2%	28.49 ± 4.46
5-10% loss	8.8%	30.44 ± 3.79	11.2%	26.96 ± 3.83
± 5%	38.0%	29.07 ± 4.19	40.2%	26.14 ± 3.61
5-10% gain	17.8%	27.79 ± 4.35	16.4%	25.34 ± 3.27
> 10% gain	24.3%	25.70 ± 4.62	23.0%	24.09 ± 3.66

Tab. III. Incidence rate (IR) of diabetes (per 100,000 person) by baseline BMI categories and BMI change (ΔBMI) categories.

	Between baseline and 2013 survey								
ΔBMI categories	Normal/underweight (< 25 kg/m^2) n = 513			Overweight (25-29.9 kg/m^2) n = 648			Obese (≥ 30kg/m^2) n = 396		
	#cases	IR	95% CI	#cases	IR	95% CI	#cases	IR	95% CI
> 10% loss	3	148.03	47.7-459.0	9	241.02	125.4-463.2	23	360.05	239.3-541.8
5-10% loss	2	97.01	24.3-387.9	14	249.30	147.6-420.9	12	285.47	162.1-502.7
± 5%	20	161.78	104.4-250.7	42	192.62	142.3-260-6	38	307.84	224.0-423.1
5-10% gain	10	144.54	77.8-268.6	27	272.94	187.2-398.0	11	322.39	178.5-582.1
> 10% gain	20	125.33	80.9-194.3	20	244.28	157.6-378.6	10	248.69	133.8-462.2

group at baseline was 47.33, 47.37 and 46.39 years which indicate that the majority of the study population has been middle-aged, conducting similar surveys in younger population studies might show different results. The overall IR of diabetes mellitus between the three categories of Normal BMI, Overweight, and Obese was the highest in Obese (≥ 30 kg/m^2) participants and the lowest in those with Normal BMI (< 25 kg/m^2). Based on BMI categories, participants with minimal BMI change (± 5%) and normal BMI at baseline, 5-10% weight gain and overweight at baseline, and obese subjects at baseline with more than 10% weight loss showed the highest IR (non-significant) for DM after 13 years follow up. When assessing the relationship between BMI changes and the incidence of DM, a specific pattern was not seen after analysis, and the hazard ratio (HR) does not show a significant positive or adverse effect on any of the categories or subgroups.

In the current study, the majority of women were in overweight and obese groups (40.7% and 36.8%) while the majority of men were in normal and overweight groups (43.3% and 42.5%) at baseline. Participants with normal BMI were more likely to be smokers, more physically active, and have healthier diets. After follow-up, the mean BMI changes for participants with normal BMI and overweight were positive, meaning weight gain for these groups, and for participants with obesity, the mean changes were negative, meaning weight loss for this group. Mean BMI changes in the obese group were greater for men than women (2.72 ± 12.29% compared to 0.84 ± 11.11%). Overall, the majority of the study population (both men and women) experienced minimal BMI changes (± 5%). In a similar study of Alberta's Tomorrow project cohort, the demographic features of the study population are similar to the current study, in which the majority of current smokers are in the normal BMI group (15.7% compared to 12.9 and 11.6), although the results for former smokers is the opposite (40.5% in the obese group compared to 35.1% and 28.1% for overweight and normal BMI). Also, participants with normal BMI are more physically active (52.7%) and have healthier diets. In the mentioned study, BMI had increased in participants with overweight and obesity at baseline it showed to be associated with an increased risk of diabetes incident, and BMI decreased associated with decreased risk of diabetes incident. On the other hand, BMI changes in participants with normal BMI show no significant relation with the risk of diabetes

incidents [29].

In another study of the 20-year China Health and Nutrition Survey risk of DM, the incidence was increased in participants with weight gain compared to minimal BMI change, especially with rapid and significant weight gain rather than moderate weight gain [30]. Another study of the Japanese population showed an increase of BMI by 1 kg/m^2 is associated with a 25% increase in the risk of diabetes incidence, even for participants with normal BMI at baseline [31]. Similar results were reported in a cohort study by Oguma et al., which demonstrated weight gain as a risk factor for diabetes, even in individuals with normal BMI at baseline [20]. The study of Koh-Banerjee et al., on US men, demonstrated every 1 kg of weight gain increases the risk of diabetes by 7.3% [32]. The study of MY Health Up Study done by Kaneto et al., demonstrated that long-term weight gain in adults is an indicator of developing diabetes in the future, even weight gain within the limits of normal BMI is associated with an increased risk of diabetes [18]. The meta-analysis of Kodama et al. suggested weight gain as a predictor of developing type 2 diabetes, especially in early adulthood in comparison to middle or late adulthood [33]. The same results, conducted from other studies such as Colditz et al., and French et al., demonstrated weight gain as a predictor of diabetes incidence. In the current study, although not statistically significant, moderate weight gain (5-10% of baseline body weight) in overweight participants is associated with the highest incidence rate of diabetes in that group [8, 21].

On the other hand, some studies showed weight loss can have a protective effect on developing diabetes, such as the study by Wing et al., after 2 years of interventions on diet and exercise [14]. In the meta-analysis of Karla et al., after pooling 63 studies into the meta-analysis, it is shown that even a small reduction of weight is associated with reduced risk of diabetes, (every 1 kg of weight loss is associated with lowering the odds of diabetes by 43%) [34]. In the trials of Kosaka et al., Long et al., Penn et al., Knowler, et al., and Lindstro et al., similar results are conducted [10-13, 15]. In a nationwide Korean study undertaken by Kim et al., no significant relations between increased BMI and incident diabetes was seen, however, weight loss was significantly associated with lower risk of diabetes [35].

Some studies suggest weight changes even weight loss is a risk factor for developing chronic diseases such as

Tab. IV. Association between BMI changes (ΔBMI) and incidence rate of diabetes: results from multivariable Cox regression.

Total participants n = 1557	*Model 1 HR (95% CI)	**Model 2 HR (95% CI)	***Model 3 HR (95% CI)
ΔBMI (absolute) Per kg/m²	1.00 (0.99-1.01)	1.00 (0.99-1.00)	0.99 (0.99-1.00)
ΔBMI (relative) Per 10%	1.00(0.99-1.01)	1.00(0.99-1.00)	0.99(0.99-1.00)
Relative ΔBMI (category)			
> 10% loss	0.96 (0.63-1.46)	0.95 (0.62-1.45)	0.93 (0.61-1.41)
5-10% loss	1.11 (0.75-1.64)	1.05 (0.70-1.55)	1.14 (0.76-1.69)
± 5%	1 (-)	1 (-)	1 (-)
5-10% gain	1.05 (0.74-1.49)	1.08 (0.76-1.54)	1.13 (0.80-1.61)
> 10% gain	0.77 (0.55-1.09)	0.77 (0.55-1.09)	0.83 (0.59-1.17)
Subgroup 1: Normal/underweight at the baseline n = 513			
ΔBMI (absolute) Per kg/m²	0.99 (0.97-1.01)	0.99 (0.97-1.01)	0.99 (0.97-1.01)
ΔBMI (relative) Per 10%	0.99(0.97-1.01)	0.99(0.97-1.01)	0.99(0.97-1.01)
Relative ΔBMI (category)			
> 10% loss	0.47 (0.11-2.01)	0.51 (0.11-2.19)	0.55 (0.12-2.38)
5-10% loss	0.89 (0.26-3.03)	0.72 (0.21-2.48)	0.77 (0.22-2.66)
± 5%	1 (-)	1 (-)	1 (-)
5-10% gain	0.89 (0.41-1.91)	1.02 (0.47-2.21)	1.08 (0.49-2.36)
> 10% gain	0.75 (0.40-1.40)	0.76 (0.41-1.44)	0.80 (0.43-1.51)
Subgroup 2: overweight at the baseline n = 648			
ΔBMI (absolute) Per kg/m²	0.99 (0.97-1.01)	0.99 (0.97-1.00)	0.99 (0.97-1.00)
ΔBMI (relative) Per 10%	0.99(0.97-1.01)	0.99(0.97-1.00)	0.99(0.97-1.00)
Relative ΔBMI (category)			
> 10% loss	1.21 (0.66-2.23)	1.18 (0.64-2.17)	1.14 (0.62-2.09)
5-10% loss	1.20 (0.58-2.48)	1.05 (0.49-2.21)	1.02 (0.48-2.18)
± 5%	1 (-)	1 (-)	1 (-)
5-10% gain	1.28 (0.78-2.09)	1.32 (0.81-2.17)	1.36 (0.83-2.23)
> 10% gain	1.15 (0.67-1.96)	1.18 (0.69-2.03)	1.22 (0.71-2.10)
Subgroup 3: obese at the baseline n = 396			
ΔBMI (absolute) Per kg/m²	0.98 (0.97-1.00)	0.98 (0.96-1.00)	0.98 (0.96-1.00)
ΔBMI (relative) Per 10%	0.98(0.97-1.00)	0.98(0.96-1.00)	0.98(0.96-1.00)
Relative ΔBMI (category)			
> 10% loss	0.78 (0.40-1.50)	0.77 (0.39-1.49)	0.78 (0.40-1.53)
5-10% loss	0.85 (0.50-1.44)	0.78 (0.45-1.33)	0.91 (0.53-1.58)
± 5%	1 (-)	1 (-)	1 (-)
5-10% gain	1.13 (0.58-2.23)	1.27 (0.64-2.50)	1.29 (0.65-2.56)
> 10% gain	0.81 (0.40-1.64)	0.90 (0.44-1.81)	0.96 (0.47-1.96)

*Model 1: Rare analysis, no adjustments; **Model 2: Adjusted with age and sex; ***Model 3: adjusted with age, sex, parental history of diabetes, smoking status, healthy eating index and physical activity.

diabetes type 2. In the study of Higgins et al., weight loss is shown to be associated with reducing the risk of high blood pressure and cholesterol but does not decrease the incidence of diabetes [19]. In the Cohort of Kaneto et al., weight gain has a significant effect on diabetes incidence, but a weight loss of more than 2 kg does not show any significant relations with diabetes incidence compared to moderate weight loss [18]. Conflicting results are also seen in the study of Oguma et al., although in this study weight gain is associated with an increased risk of diabetes, weight loss in early adulthood is not significantly related to diabetes incidence [20]. Also in the Iowa Women's Health Study done by French et al., BMI change is associated with an increased risk of chronic diseases such as diabetes, and even weight loss can increase the risk of developing diabetes [21]. In

this study although not statistically significant, weight loss of more than 10% of basal body weight in obese participants is associated with an increased incidence rate of diabetes. These results are almost consistent with the findings of our study. Although most of the mentioned studies showed a direct link between weight gain and DM incidence, the paradoxical role of weight loss or its ineffectiveness cannot be ignored. The justification for these contradictions can be explained by the baseline weight and BMI, the patient's age, and the presence of other risk factors [21].

Conclusions

This cohort study in the Middle East region showed that there was no significant association between diabetes mellitus incidence and BMI changes. This survey also indicated that there was no specific pattern in weight changes and diabetes outbreaks.

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Informed consent statement

The study's ethical approval was contained by the Ethical Committee of Isfahan Cardiovascular Research Center, a WHO collaborating center, and informed consent has been obtained from all participants.

Conflict of interest statement

None.

Authors' contrubutions

RSM, MKA: conceptualization; RSM, MKA, MS: methodology; RSM, AS: investigation and literature search; MT, MKA, MS, HR: data curation; RSM, AS: writing-original draft; MKA, MS: writing-review and editing.

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