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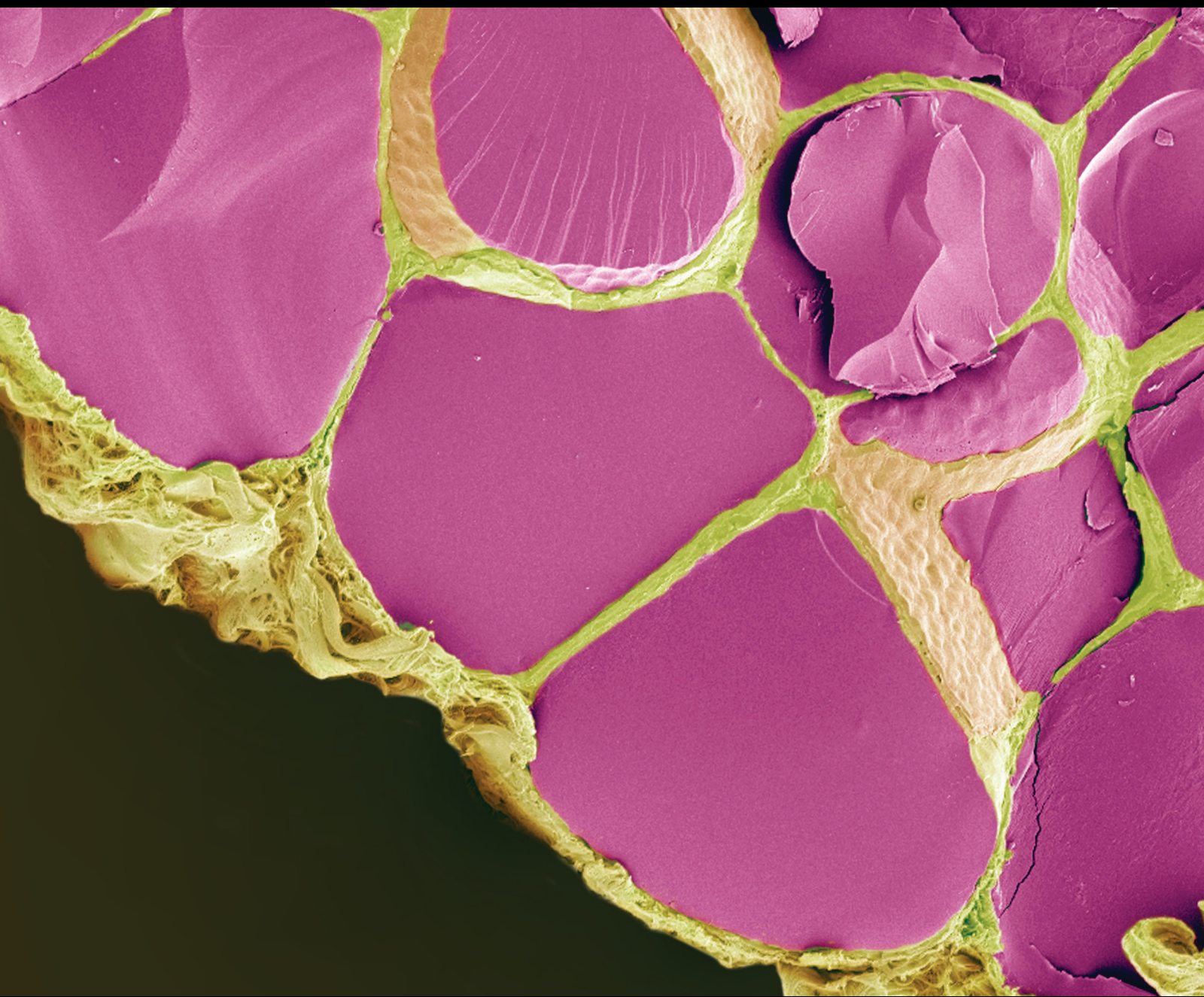
Type 2 Diabetes and Cardiovascular Risk in Women 2016

Lead Guest Editor: Alexandra Kautzky-Willer
Guest Editors: Giovannella Baggio, Maria Chiara Rossi, Annunziata Lapolla, and Giuseppina T. Russo



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Editorial Board

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Editorial

Type 2 Diabetes and Cardiovascular Risk in Women 2016

Alexandra Kautzky-Willer,[1,2] Giovannella Baggio,[3] Maria Chiara Rossi,[4] Annunziata Lapolla,[5] and Giuseppina T. Russo[6]

[1]*Gender Medicine Unit, Division of Endocrinology and Metabolism, Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria*
[2]*Gender Medicine Institute, Gars am Kamp, Austria*
[3]*Chair of Gender Medicine, Molecular Medicine Department, University of Padova, Padova, Italy*
[4]*Center for Outcomes Research and Clinical Epidemiology (CORESEARCH), Pescara, Italy*
[5]*Department of Medicine, University of Padova, Padova, Italy*
[6]*Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy*

Correspondence should be addressed to Alexandra Kautzky-Willer; alexandra.kautzky-willer@meduniwien.ac.at

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Due to population growth and ageing, diabetes is now among the 8 leading causes of death [1]. Thus, type 2 diabetes comprising the majority of diabetic patients is one of the most important NCDs and its steep rise and associated complications go along with mounting evidence of clinically important sex and gender differences [2]. Genetic background, lifestyle, epigenetics, and environment contribute to the pandemic increase with important biological and psychosocial risk factors of men and women. Overall, globally, more men are diagnosed with diabetes as there were 15.7 million more men than women with diabetes in 2015 [3]. There are large sex-ratio differences regarding diabetes across countries which parallel those of obesity, the most prominent risk factor in both sexes. Type 2 diabetes is more frequently and at a younger age and lower body-mass-index (BMI) diagnosed in males as men usually feature more visceral fat and higher degree of insulin resistance compared to women of comparable age and BMI. However, waist is a better predictor of diabetes and cardiovascular disease in women who also have a greater relative risk of cardiovascular complications and mortality in the presence of prediabetes, the metabolic syndrome, or overt diabetes [4, 5]. Altogether, diabetic women bear a greater risk to suffer and die from myocardial infarction or stroke than men in comparison to same sex nondiabetic subjects [6].

Diversities in biology, culture, lifestyle, and socioeconomic status impact sex dimorphism in clinical presentation of type 2 diabetes. Biological differences comprise differences in body composition, glucose and fat metabolism, energy balance, and neuroendocrine regulation [2]. In particular, reproductive history and reproductive factors are important for evaluation of diabetes and cardiovascular risk. Thus, women with early menarche, irregular cycles, or the PCOS were shown to be at higher risk. However, the most important risk factor in women appears to be gestational diabetes which affects approximately 10% of all pregnant women and is associated with both acute and long-term complications in mothers and offspring. Therefore, sex-specific guidelines for stroke prevention in women were recently released outlining the importance of gestational diabetes and preeclampsia as sex-specific risk factors and the impact of diabetes, depression, and psychosocial stress as risk factors particularly in females [7]. Differences in therapy and interventions further contribute to different outcomes in diabetic patients with greater disparities in women [8].

Therefore, the issue of prevention and therapy of cardiovascular disease is of utmost importance for health-related quality of life of diabetic women. To this end, this special series will cover interesting papers on this important topic summarizing current evidence and further expanding our present knowledge.

One paper describes the incidence of stroke and stroke subtypes derived from the stroke and diabetes surveillance system in China. L. Guo et al. report almost fourfold excess risk in diabetic patients, especially in females and particularly regarding the subtype cerebral infarction.

Another study by M. Leutner et al. analysed metabolic and vascular characteristics of treated hyperlipidemic men and women. Overall, vascular morphology, insulin sensitivity, and glucose tolerance did not differ between sexes although women had a more favourable lipid profile and better liver enzymes.

In addition, a review by G. T. Russo et al. will address the important topic of osteoporosis and fracture risk based on experimental and clinical evidence in men and women with diabetes. Both sex differences in pathophysiology and lifestyle and gender implications including the side effects of glucose-lowering drug therapies will be discussed.

Further, a review by S. Burlina et al. will present and discuss the current evidence of cardiovascular risk in women with gestational diabetes. This is important as this growing number of women could present an ideal group for sex-specific diabetes and cardiovascular prevention programs. Early identification of those women at the highest risk could reduce the burden of transgenerational diabetes.

We hope that this special series will further highlight the importance of cardiovascular risk in diabetic women, stimulate new research, and contribute to better awareness and care.

Alexandra Kautzky-Willer
Giovannella Baggio
Maria Chiara Rossi
Annunziata Lapolla
Giuseppina T. Russo

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Research Article

Sex Differences in the Effect of Type 2 Diabetes on Major Cardiovascular Diseases: Results from a Population-Based Study in Italy

Paola Ballotari,[1,2] Francesco Venturelli,[3] Marina Greci,[4] Paolo Giorgi Rossi,[1,2] and Valeria Manicardi[5]

[1]*Interinstitutional Epidemiology Unit, Local Health Authority of Reggio Emilia, Via Amendola 2, 42122 Reggio Emilia, Italy*
[2]*Arcispedale Santa Maria Nuova-IRCCS, Reggio Emilia, Viale Umberto I 50, 42123 Reggio Emilia, Italy*
[3]*Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Via Campi 287, 41126 Modena, Italy*
[4]*Primary Care Department, Local Health Authority of Reggio Emilia, Via Amendola 2, 42122 Reggio Emilia, Italy*
[5]*Internal Medicine Department, Montecchio Hospital, Local Health Authority of Reggio Emilia, Via Barilla 16, 42027 Montecchio, Italy*

Correspondence should be addressed to Francesco Venturelli; venturelli.dr.francesco@gmail.com

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The aim of the study is to assess sex difference in association between type 2 diabetes and incidence of major cardiovascular events, that is, myocardial infarction, stroke, and heart failure, using information retrieved by diabetes register. The inhabitants of Reggio Emilia (Italy) aged 30–84 were followed during 2012–2014. Incidence rate ratios and 95% confidence intervals were calculated using multivariate Poisson model. The age- and sex-specific event rates were graphed. Subjects with type 2 diabetes had an excess risk compared to their counterparts without diabetes for all the three major cardiovascular events. The excess risk is similar in women and men for stroke (1.8 times) and heart failure (2.7 times), while for myocardial infarction, the excess risk in women is greater than the one observed in men (IRR 2.58, 95% CI 2.22–3.00 and IRR 1.78, 95% CI 1.60–2.00, resp.; P of interaction < 0.0001). Women had always a lesser risk than men, but in case of myocardial infarction, the women with type 2 diabetes lost part of advantage gained by women free of diabetes (IRR 0.61, 95% CI 0.53–0.72 and IRR 0.36, 95% CI 0.33–0.39, resp.). In women with type 2 diabetes, the risk of major cardiovascular events is anticipated by 20–30 years, while in men it is by 15–20.

1. Introduction

In the list of the top ten killers created by the Global Burden of Disease study, ischemic heart disease and stroke contended for first place, causing 13% and 12% of the total deaths in 2012, respectively. Moreover, the WHO estimated that ischemic heart disease contributed to a third of the 96.4% increase in the prevalence of heart failure (HF) from 1990 to 2013 worldwide [1].

Accordingly, the European Society of Cardiology (ESC) identifies cardiovascular diseases (CVDs) as the leading cause of death in Europe. In a recent issue, the ESC estimated that, despite recent decreases in mortality rate in many countries, close to half deaths in Europe in 2014 are attributable to CVDs, with a higher proportion in women (51%) than in men (42%) [2].

The WHO also identified diabetes as the fifth and ninth cause of deaths in women and men, respectively [1]. Indeed, diabetes is a major public health issue with an increasing prevalence globally, affecting at least 8% of the adult population worldwide [3].

Cardiovascular diseases, including coronary heart disease (CHD), stroke, and heart failure, are predominant causes of morbidity and mortality among people with diabetes [4].

Conversely, diabetes increases the prevalence of most of the main risk factors for CVDs, leading to an increased risk

of related morbidity and mortality [5–12]. However, accruing evidence highlights that women and men experience the disease differently [13, 14]. Actually, women lose their relative protection from CVDs, and postmenopausal diabetic females, compared to the general population, presented a stronger increase of cardiometabolic risk than diabetic males, but the reasons are not entirely clear [15–18]. The explanations are likely to be multifactorial, with contributions from differences in inherent physiological factors and in the management and treatment of diabetes, to the detriment of women [19, 20].

The data collected by the Italian Society of Diabetologists (AMD) on quality of diabetes care and gender difference in access to effective care in Italy, show, in a large population of type 2 diabetes, that gender disparities in control of the disease are less pronounced in Italy than in other countries, but they still exist, despite equity of access to specialist care and the same pharmacological treatment of women and men [21].

A specific negative interaction between being a woman and having diabetes in CVDs risk was supported by most of the studies [22–25] but questioned by some other authors [18, 26]. The inconsistency of evidence could be partly due to several limitations such as failure to distinguishing between types of diabetes or selection bias in observational studies or extremely selected populations in trial participants [27, 28]. Large register-based studies which identify the different types of diabetes are required to examine differences between sex in CVD occurrence and mortality in the general population.

In the Reggio Emilia province, the Diabetes Register (REDR) was set up since 2009 and is able to ascertain cases and to distinguish the type of diabetes [29].

The present study aims to assess sex differences in the association between type 2 diabetes (T2D) and incidence of major cardiovascular diseases (CVDs), that is, myocardial infarction, stroke, and heart failure, using the REDR information.

2. Materials and Methods

2.1. Setting and Study Population. This is a cohort study where all residents in the Reggio Emilia province, Italy, as of December 31st, 2011 (approx. 0.5 million inhabitants), aged 30–84, were followed during 2012–2014 period. The follow-up lasted until the date of first CVD event, all-causes death, emigration, or end of follow-up (as of December 31st, 2014), whichever occurred first.

The residence and vital status information was retrieved from the civil register, as well as T2D status from the Reggio Emilia Diabetes Register (REDR).

The REDR is a validated database created by the deterministic linkage of six routinely collected data sources through a definite algorithm able to ascertain cases and to distinguish type of diabetes and model of care [29]. Data have been included since 2009, and the REDR is updated annually. The date of inclusion in the register is the date when a person first meets one of the following inclusion criteria: (1) disease-specific exemption database: exemption from copayment due to diabetes; (2) hospital discharge database: hospitalization with diabetes diagnosis in whichever position by ICD-9 (International Classification of Diseases Clinical Modification, 9th Edition) codes 250.xx, 357.2x, 362.0x, 366.41, and 648.0x, excluding MDC14; (3) biochemistry laboratory database: one glycated haemoglobin (HbA1c) test $\geq 6.5\%$ (48 mmol/mol); (4) drug prescription databases: redeemed prescription at least twice for antidiabetic drugs in case of pharmacy distribution, only one in case of direct distribution; (5) diabetes outpatient clinics database: diagnosis by a diabetologist; and (6) Reggio Emilia mortality register: cause of death by ICD-10 (International Classification of Diseases, 10th Edition) codes E10–E14. Women with gestational diabetes or women receiving treatment for polycystic ovarian syndrome were excluded.

The type of diabetes, suggested by the presence of defined criteria as described elsewhere [29], was confirmed by a diagnosis provided by a diabetologist or another physician.

Subjects included in the register with type 1 diabetes or secondary diabetes (i.e., drug-induced diabetes, diseases of exocrine pancreas, etc.) or with undefined diabetes were excluded from the analysis.

2.2. Outcomes and Other Variables. The outcomes were the first event between hospitalization and death for stroke, myocardial infarction, and heart failure. Fatal events were considered cases in which only the death certificate was present or cases with hospitalization followed by a death certificate for the same cause during the study period. The outcomes were defined according to the International Classification of Disease, 9th Revision (ICD-9) in case of nonfatal event and 10th Revision (ICD-10) in case of fatal event: (1) nonfatal stroke (ICD-9 codes 430–434) or death from cerebrovascular disease (ICD-10 codes I60–I63); (2) nonfatal myocardial infarction (ICD-9 codes 410-411) or deaths from myocardial infarction (ICD-10 codes I21, I22, I24.8, I24.9); and (3) heart failure requiring hospitalization (ICD-9 code 428) or causing death (ICD-10 code I50).

Data were retrieved from hospital discharge database in case of nonfatal events, using primary diagnosis and excluding day hospital, and from Reggio Emilia mortality register for deaths. Each participant could contribute only once to incidence of each event, that is, with first event detected in the study period, but the same subject could contribute for more types of outcome.

Individual demographic information included age, sex, and foreign status (i.e., non-Italian citizenship).

2.3. Statistical Methods. The characteristics of the study population are presented as median and proportions and stratified by sex and T2D status. The event numbers and person-time at risk were calculated for each major CVD examined.

Age-adjusted event rates (AAER) per 10,000 with 95% confidence intervals (95% CI) by sex and T2D status for each type of event were estimated using the Italian population as of December 31st, 2011, as a reference for standardization [30]. Incidence rate ratios (IRR) and 95% confidence intervals (95% CI) for the risk of each CDV in people with T2D versus the population without diabetes were calculated using multivariate Poisson regression models and stratifying by sex. The effect modification of sex on the association between T2D and CVDs was tested using the Wald test. Finally,

Table 1: Baseline characteristics of the study cohorts, age 30–84, Reggio Emilia—Italy, as of December 31st, 2011.

	Men		Women	
	Without T2DM	With T2DM	Without T2DM	With T2DM
Inhabitants				
Total, *n*	161,045	13,714	170,798	10,634
Foreigners, *n* (%)	17,444 (10.8)	907 (6.6)	19,336 (11.3)	846 (8.0)
Age (years): median (IQR)	48 (39–61)	67 (58–74)	50 (40–64)	70 (61–77)

T2D = type 2 diabetes.

the age-specific event rates stratified by sex for individuals with and without diabetes were graphed.

The analyses were performed using the STATA statistical package Version 13.0.

3. Results

On December 31st, 2011, the REDR included 14,531 and 12,424 prevalent men and women with T2D, respectively. The overall prevalence is 5.7% and 4.7%, respectively. Restricting to people aged 30–84, 13,714 men and 10,634 women (44% out of the total) with T2D were included in our study (Table 1). The median age of the diabetic population is about 20 years higher than the people without diabetes.

During the 3-year follow-up, the number of fatal events was higher for myocardial infarction than for other CVDs (Table 2) (9.6% and 9.1% for men and women, resp., with no difference between the two sexes). Among men without T2D, myocardial infarction was the most frequent CVD, closely followed by stroke and remotely by heart failure, while among women without T2D, the stroke was the most frequent CVD, followed by myocardial infarction and heart failure, both halved with respect to the former.

Performing the analysis without sex stratifications, the stroke and myocardial infarction risks in people with T2D were almost twofold higher than in those without diabetes, while heart failure risk was almost three times higher (IRR 1.84, 95% CI 1.70–1.98; IRR 2.00, 95% CI 1.83–2.18; IRR 2.70, 95% CI 2.47–2.94, resp., data not reported in the tables).

Women with T2D had 1.8 times the probability of a stroke (Table 2) than the women without diabetes (95% CI 1.61–2.04), 2.6 times the probability of having a myocardial infarction and heart failure (95% CI 2.22–3.00 and 2.27–2.97, resp.). Men with T2D have similar excess risk for stroke and heart failure, but the excess risk for myocardial infarction is lower than the one observed in women (IRR 1.78, 95% CI 1.60–2.00).

The relative risk for myocardial infarction associated with T2D was significantly greater in women than in men ($P < 0.0001$), while there is no evidence of sex difference for the stroke and heart failure ($P = 0.9151$ and $P = 0.9289$, resp.). Women free of diabetes had lesser risk than men free of diabetes to experience whichever CVD events (Table 3). The reduction is 30% in case of stroke and heart failure and 60% in case of myocardial infarction. Women with type 2 diabetes had also lesser risk than men with type 2 diabetes to experience whichever CVD events, but in case of stroke and heart failure, the reduction percentages were similar to those found comparing sex free of diabetes; meanwhile, in case of myocardial infarction, the reduction is only 30% (instead of 60%).

The foreigners seemed to have similar risk of stroke (in people with T2D IRR 0.93, 95% CI 0.62–1.40; in people without T2D IRR 0.90, 95% CI 0.72–1.12) and heart failure (in people with T2D IRR 0.76, 95% CI 0.45–1.28; in people without T2D IRR 0.98, 95% CI 0.69–1.40), while in case of myocardial infarction, a protective effect was found in the population without T2D, but not in those with T2D (in people with T2D IRR 1.03, 95% CI 0.71–1.48; in people without T2D IRR 0.68, 95% CI 0.54–0.86). The same pattern was observed in men and women.

In the women without diabetes, the risk is virtually zero until 54 yrs for myocardial infarction, until 60 for stroke and until 70 for heart failure (Figure 1; Annex 1 in Supplementary Material available online at https://doi.org/10.1155/2017/6039356), while for the men without diabetes, the risk is appreciable from the age of 45 for myocardial infarction, 50 for stroke, and 65 for heart failure. In general, the risk of CVD events in men and women with T2D starts to be noticeable at an earlier age than in the population without diabetes. The anticipation is longer in women than in men for myocardial infarction and stroke. The resulting excess risk for people with T2D is therefore higher in younger ages for all the outcomes in both sexes and, particularly, for myocardial infarction in women.

4. Discussion

In our study, people with T2D experienced an excess risk for all the investigated CVDs, that is, stroke, myocardial infarction, and heart failure. These results are consistent with many studies [13, 14] and reflect those observed for mortality in a previous analysis applied to the same population, where we found an excess risk for cardiovascular diseases in population with diabetes of both sexes, stronger in women and in particular for myocardial infarction [31].

Although we observed nondiabetic women having fewer CVD events than nondiabetic men of the same age, this advantage appears to be partially lost for myocardial infarction in the context of T2D, but not for the other two CVDs. Our results were consistent with those of a recent Italian study that showed a diabetes-related excess risk greater in women than in men for myocardial infarction but not for heart failure and stroke [32].

In a Finnish cohort study [13], the presence of diabetes reduced the so-called female advantage for CVD risk; indeed, mortality from CHD was three times higher in women compared with men with diabetes. Similar findings were

Table 2: *N* of events, person-years, and age-adjusted event rates (AAER) per 10,000 person-years and incidence rate ratios (IRR) with 95% confidence intervals (95% CI) by sex and type of event.

Events	Men							Women						
	Without T2D			With T2D				Without T2D			With T2D			
	N of events (fatal)	Person-years	AAER	*N* of events (fatal)	Person-years	AAER	IRR (95% CI)	*N* of events (fatal)	Person-years	AAER	*N* of events (fatal)	Person-years	AAER	IRR (95% CI)
Stroke	1454 (95)	475,145.4	37.28	517 (36)	38,600.9	74.70	1.86 (1.68–2.06)	1301 (115)	506,105.0	30.10	341 (22)	30,187.2	61.73	1.81 (1.61–2.04)
Myocardial infarction	1590 (217)	474,943.0	39.04	459 (60)	38,716.2	78.02	1.78 (1.60–2.00)	713 (128)	506,799.3	16.13	241 (37)	30,328.7	47.58	2.58 (2.22–3.00)
Heart failure	816 (14)	475,993.8	21.47	481 (10)	38,702.4	63.71	2.78 (2.48–3.12)	718 (17)	506,803.8	17.10	306 (10)	30,262.9	48.83	2.59 (2.27–2.97)

Age-adjusted event rates were calculated using Italian population at December 31st, 2011, stratified by sex.
IRR = calculated using Poisson model, adjusted for age and foreign status. People without type 2 diabetes were used as reference.

Table 3: Incidence rate ratios (IRR) with 95% confidence intervals (95% CI) by type 2 diabetes status and type of event, women versus men.

Women versus men	Without T2DM		With T2DM	
	IRR	95% CI	IRR	95% CI
Stroke	0.68	0.63–0.74	0.72	0.62–0.82
Myocardial infarction	0.36	0.33–0.39	0.61	0.53–0.72
Heart failure	0.63	0.57–0.69	0.66	0.58–0.77

IRR = calculated using Poisson model, adjusted for age and foreign status. Men were used as reference.

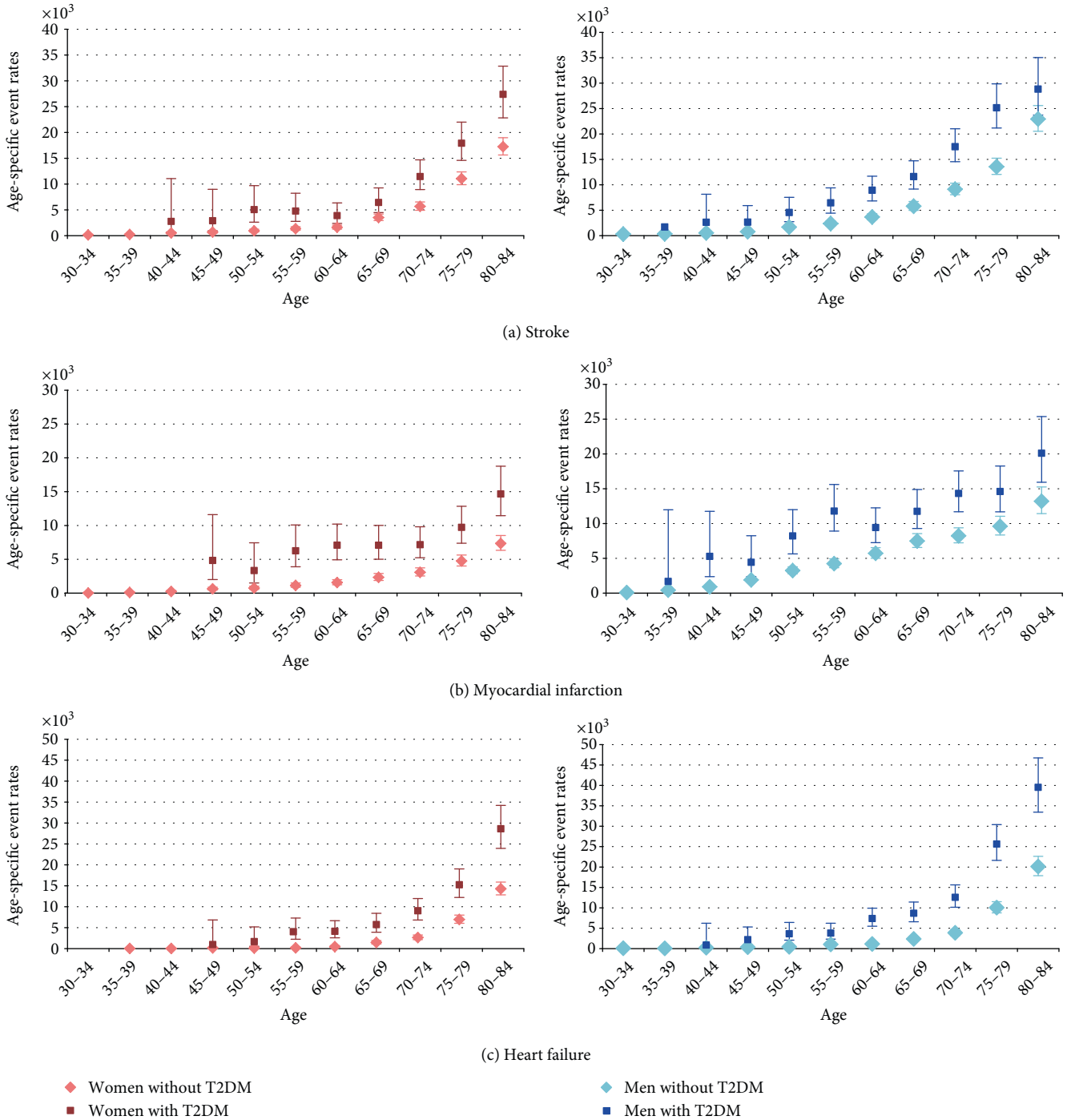

Figure 1: Age-specific event rates by sex, type 2 diabetes status, and type of event.

observed in the NHANES cohort [33] and in the study based on UK General Practice data [34], the latter investigating subsequent myocardial infarction. The stronger impact of diabetes as a major risk factor for CVD events in women than men, 4.3-fold risk compared to 2.7, is described also in the INTERHEART, an international case-control study including 15,152 cases and 14,820 controls from 52 countries [35]. On the other hand, a systematic review showed that the risk of incident CHD was three times higher in women with diabetes than in women without diabetes, while the risk in men doubled [36]. A similar difference in the excess of risk, 50% more, was found in a previous systematic review [15].

We observed a risk of heart failure almost 3 times higher in the presence of T2D, similar to results found in Oregon [10] and in Iceland [37], but in our study, the overall excess risk was similar in women and men ($P = 0.9245$). In the Framingham Heart Study [25], the heart failure risk was 2 times higher in men and 5 times higher in women with diabetes compared with the general population.

Also, in case of stroke, we found an excess risk for T2D but no sex difference in the excess ($P = 0.9197$). The results of individual studies on the sex differences on the risk of stroke associated with diabetes have been inconsistent, with some studies showing women with diabetes had higher [13, 25, 38, 39], similar [40], or lower risk [41, 42] compared to men with diabetes. In a recent comprehensive systematic review and meta-analysis using data from 64 cohorts [20], the pooled analysis shows a significantly higher relative effect of diabetes on stroke risk in women compared to men, even adjusting for other major cardiovascular risk factors. As suggested by other authors [32], the different prevalence of medical condition underlying the physiopathology of stroke (i.e., arterial hypertension and atrial fibrillation) between sexes [43] may reduce the difference in the gender-related diabetes risk for stroke and myocardial infarction.

This greater excess coronary risk may be explained by more adverse cardiovascular risk profiles among women with diabetes, combined with possible disparities in treatment and quality of care that favor men. A recent review explored biological and environmental factors that play a role in the reduction of the protective effect of female sex from CVD in diabetic women [44]. The authors pointed out the interaction between insulin and the estrogen signaling and the effect of hyperglycemia on the expression and activity of estrogen receptors as mechanisms underlying the diabetes-related impairment of endothelium in diabetic women. The resulting proinflammatory environment accelerates the atherosclerotic process that leads to coronary arteries disease, particularly in women.

In two large population studies carried out in Italy [21, 45], subjects with T2D—included the majority of the population enrolled our study—were investigated to ascertain whether gender differences in quality of care of diabetes exist in Italy [21]. The authors found that the likelihood to reach specific clinical outcomes is systematically unfavorable for women as compared with men, although the disparities are less pronounced than in other countries.

Many international studies documented a systematic undertreatment of cardiovascular risk factors in diabetic women: the results of the DIANA study [46] indicated that men with diabetes were significantly more likely to receive any treatment for the major CVD risk factors, including oral hypoglycemic agents, ACE inhibitors, and calcium channel blockers for CHD, than women. Evidence has emerged demonstrating a potential sex disparity in the intensity of cardiovascular risk reduction, whereby worse glycated hemoglobin control, lower frequency of lipid-lowering therapy, lower aspirin use, and lower blood pressure control were noted in women [47].

In contrast with these international data [48], women with diabetes in Italy are not undertreated with medications for cardiovascular risk factors. Also in the study of Rossi et al. [21], the proportion of diabetic women treated with insulin, statins, or antihypertensive agents was equal to or even higher than that of men. The MIND-IT (Multifactorial Intervention in Type 2 Diabetes in Italy)—a cross-sectional study that enrolled over 2,000 type 2 diabetic patients without previous described CVD events—investigated the degree of control of CVD risk factors [49]: diabetic women showed a worse CVD risk profile, with a less percentage of diabetic women reaching the recommended metabolic targets compared to men, regardless of use of medications for CVD risk factors control. In the light of reported evidence, we suggest that both the diverse physiopathology and the systematic use of ACE inhibitors or B-blockers and statins in Italian diabetic patients, without gender differences, might explain the lack of differences in stroke and heart failure risk between men and women.

The age curves of risk show that in the population with T2D the incidence is brought forward by 20–30 years in women and by 15–20 years in men for stroke and myocardial infarction, while for the heart failure, a marked anticipation of the onset can be observed for both sexes (Figure 1; Annex 1 in Supplementary Material). Consequently, the incidence of stroke and myocardial infarction in young ages is several times higher than the one in the population without diabetes, while in people over 70, it is only 2- or 1.5-fold. This is particularly true for women, because the incidence of stroke and myocardial infarction in the population without diabetes remains virtually null before the age of 60. The results are consistent with a previous study [13] in Finland.

4.1. Strengths and Limitation. The population-based cohort study approach increases the external validity, and the use of diabetes register reduces the ascertainment bias. Indeed, the study excludes cases of type 1 diabetes (732), secondary diabetes (137), or undefined diabetes (901), maximizing the accuracy in the definition of the two subcohorts (i.e., with and without T2D).

Although the AHA statement notes possible sex differences in cardiovascular outcomes within racial/ethnic groups, our study did not have sufficient power to analyze differences by geographical origin, although we use this covariate in multivariate model. In addition, we could not control for other cardiovascular risk factors in the analysis, because unlike observational studies of patients from clinical databases, there is only limited clinical information on the general population; hence, it is not possible to provide a detailed clinical

characterization of the general population. We foresee a second study to investigate the determinants of CVD events only in population with T2D using different clinical information as well as prescribed drug and information on other areas of care such as tests and lifestyle factors and diabetes duration.

5. Conclusions

Women with T2D have earlier risk of major cardiovascular events by 20–30 years and males by 15–20 compared to the people without diabetes. The overall incidence of myocardial infarction, stroke, and heart failure is about twofold in T2D compared to the people without diabetes. The diabetes-related excess risk of myocardial infarction is much higher for women than for men, while for the other CVDs, people with T2D of the two sexes have a similar excess risk. In light of finding possible mechanisms to explain the partial loss of advantage for myocardial infarction and not for the other two types of events, we foresee a second study to investigate the determinants of CVD events only in population with T2D using information about prescribed drug and on other areas of care such as tests and lifestyle factors and diabetes duration.

Ethical Approval

This is an observational study and the data were collected retrospectively. The Local Health Authority of Reggio Emilia was responsible for collecting and processing the data. The REDR has been approved by the provincial Ethic Committee on July 23rd, 2014. The aim of the study is consistent with the specific objective of the REDR as approved by the Ethic Committee. According to Italian privacy law, no patient or parental consent is required for large retrospective population-based studies approved by the competent Ethic Committee, if data are published only in aggregated form.

Competing Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Review Article

Fracture Risk in Type 2 Diabetes: Current Perspectives and Gender Differences

Giuseppina T. Russo, Annalisa Giandalia, Elisabetta L. Romeo, Morabito Nunziata, Marco Muscianisi, Maria Concetta Ruffo, Antonino Catalano, and Domenico Cucinotta

Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy

Correspondence should be addressed to Giuseppina T. Russo; giuseppina.russo@unime.it

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Type 2 diabetes mellitus (T2DM) is associated with an increased risk of osteoporotic fractures, resulting in disabilities and increased mortality. The pathophysiological mechanisms linking diabetes to osteoporosis have not been fully explained, but alterations in bone structure and quality are well described in diabetic subjects, likely due to a combination of different factors. Insulin deficiency and dysfunction, obesity and hyperinsulinemia, altered level of oestrogen, leptin, and adiponectin as well as diabetes-related complications, especially peripheral neuropathy, orthostatic hypotension, or reduced vision due to retinopathy may all be associated with an impairment in bone metabolism and with the increased risk of fractures. Finally, medications commonly used in the treatment of T2DM may have an impact on bone metabolism and on fracture risk, particularly in postmenopausal women. When considering the impact of hypoglycaemic drugs on bone, it is important to balance their potential direct effects on bone quality with the risk of falling-related fractures due to the associated hypoglycaemic risk. In this review, experimental and clinical evidence connecting bone metabolism and fracture risk to T2DM is discussed, with particular emphasis on hypoglycaemic treatments and gender-specific implications.

1. Introduction

Osteoporosis, literally "porous bone," a disease characterized by weak bone, is a major public health problem, affecting hundreds of millions of people worldwide, predominantly postmenopausal women. In the general population, prevalence of osteoporosis and incidence of osteoporotic fractures are considerably higher in women than in men [1], because of higher bone mineral density, greater bone size, and hence a stronger bone structure in male gender [2].

Sex hormones play a central role in the physiology of bone by direct and indirect mechanisms and the abrupt loss of estrogens at menopause onset is considered the major reason for primary osteoporosis in women; conversely, a dramatic loss of androgens with aging is lacking in men [2]. The main clinical consequences of the disease are bone fractures, especially at the hip and spine, which may be associated with serious complications such as substantial pain, disability, and even death. Dual energy X-ray absorptiometry (DXA) represents the gold standard for the diagnosis of osteoporosis [3]. According to the World Health Organization, among postmenopausal women and men 50 years old and older, diagnosis is based on T-score (normal values, >1.0; osteopenia, –1 to –2.5; and osteoporosis, <2.5 SD) [4].

The report "Osteoporosis in the European Union: Medical Management, Epidemiology and Economic Burden" describes the burden of osteoporosis in the EU in 2010. Twenty-two million women and 5.5 million men were estimated to have osteoporosis, with 3.5 million new fragility fractures, including 620,000 hip fractures, 520,000 vertebral fractures, 560,000 forearm fractures, and 1,800,000 fractures in other sites [1]. As a consequence, osteoporosis imposes a significant economic burden that goes beyond the medical one. Thus, the economic burden of incident and prior fragility fractures was estimated at £37 billion and these costs are expected to increase by 25% in 2025 [5].

The primary aim of pharmacological therapy is to reduce fractures risk. Although a range of medications have become

available for treatment and prevention of osteoporosis during the past 4 decades, the majority of individuals who have experienced an osteoporosis-related fracture or who are at high risk of fracture are untreated and the number of patients on treatment is declining. Finally, longevity has resulted in an increasing number of subjects at higher risk for osteoporotic fractures and its related comorbidities [1].

Type 2 diabetes (T2DM) prevalence is increasing worldwide, and this increase affects especially the elderly population. As a consequence, the number of T2DM patients with osteoporosis will further increase, posing elderly patients in a vicious circle of disability due to both increased incidence of fractures and micro- and macrovascular diabetes-related complications.

Osteoporosis is a gender-related disease and postmenopausal women with diabetes, who are a particularly fragile population because of the higher cardiovascular disease-related risk [6, 7], are those at significantly higher risk for osteoporosis and its complications [8].

This review will update current knowledge on bone metabolism and fracture risk associated with T2DM, particularly focusing on potential gender differences.

2. Fracture Risk in Type 2 Diabetes

Although osteoporosis and T2DM seem to be unrelated from a pathophysiological standpoint, a number of epidemiological studies have demonstrated an increased fracture risk among patients with T2DM.

The first studies on the association between T2DM and fractures risk produced controversial results. The Rotterdam study on 5931 subjects (2481 men and 3450 women aged ≥ 55 years, of whom 578 were T2DM) showed a greater bone mineral density (BMD) as evaluated by the DXA in T2DM patients than in subjects with normal glucose homeostasis, and a lower frequency of nonvertebral fractures among T2DM women in the 5 years prior to inclusion in the study [9]. Thus, T2DM women reported having had fewer fractures in the 5 preceding years than women without this condition (adjusted odds ratio, 0.63; 95% CI, 0.44 to 0.90), whereas the frequency of fractures in men was similar for those with and without T2DM (adjusted odds ratio, 0.96; CI, 0.60 to 1.52) [9].

Subsequent studies, on the contrary, reported an increased incidence of fractures in T2DM. In 2005, the same group of the Rotterdam study [10] reexamined the data of 6655 men and women, making a further distinction among T2DM patients who were already treated or newly diagnosed. Although people with T2DM, men and women combined, had a higher BMD, they had an increased risk of nonvertebral fractures compared with subjects without T2DM. When data were stratified by gender, a comparable trend was observed. This increase was confined to T2DM subjects already on therapy, while those with a recent diagnosis had no increase in the risk of fractures and those with glucose intolerance had even a reduction of 20 to 40% of the risk of fractures [10]. In the Health, Aging and Body Composition Study [11] (2979 subjects, 19% with T2DM, 6% with glucose intolerance) a high risk of fractures was observed (64%, relative risk RR: 1.64) among diabetic patients, while glucose intolerance was not significantly related with the risk of fractures (RR 1.34). Diabetic patients with fractures had a higher prevalence of peripheral neuropathy, TIA/stroke, and falls compared to patients with diabetes without fractures. The most common sites of fractures among diabetic patients and people with impaired glucose tolerance were the forearm (21%), vertebrae (18%), hip (18%), tibia/fibula/ankle (10%), and foot (9%). Koh et al. [12] described the association between diabetes and fracture risk in a population-based prospective cohort study of 63237 Chinese men and women who were followed up for a mean duration of 12 years. After adjustment for other major risk factors, including self-reported calcium consumption, the risk of hip fracture was significantly increased among people with diabetes compared to people without diabetes (RR, 1.98; 95% CI, 1.71–2.29), this risk increased with duration of diabetes, and the risk estimates were similar between men and women, as well as between lean and obese individuals. Also the case-control study in a Danish national database on over 120000 subjects [13] and the retrospective cohort analysis conducted on 197412 residents aged > 66 years in Canada [14] confirmed the higher fracture risk in T2DM subjects, irrespective of the use of antidiabetic agents or diabetes-related complications.

More recent large studies confirmed the tendency toward an increased fracture risk among T2DM patients, especially women. In a prospective study of 32,089 postmenopausal women, the Iowa Women's Health Study, the risk of hip fractures was 1.7 times higher among self-reported T2DM patients, after adjusting for several risk factors [15]. In the Study of Osteoporotic Fractures (SOF) T2DM participants (n = 657) had a 22% higher risk of nonspine fractures than those without T2DM (n = 8997) [16]. The Women's Health Initiative Observational Study, including 93000 postmenopausal women, of whom 5285 subjects had T2DM, prospectively followed up for 7 years, showed a significantly higher risk of fracture in several sites in T2DM women, after controlling for multiple risk factors, including a previous history of falls [17]. Similar data were observed in the longer follow-up (22 years) of the Nurses' Health Study, showing an increased risk both in type 1 diabetes mellitus (T1DM) (n = 292) and T2DM (n = 8348) [RR: 2.2 (95% CI, 1.87–2.7); after adjustment for other risk factors] [18].

Overall, fracture risk is almost two times higher in T2DM subjects compared with nondiabetic ones, both in men and in women, although most of the studies are conducted on postmenopausal women and typically considered those at higher osteoporosis risk. Epidemiological studies that specifically compared fracture risk in T2DM men versus T2DM women are not available to date, and the few indirect comparisons do not report significant gender differences. Furthermore, the dependence of fracture risk upon diabetes duration and its long-term complications is still controversial.

3. Potential Pathophysiological Basis of the Increased Fracture Risk in Type 2 Diabetes

The possible influence of T2DM on fracture risk has been explained with different mechanisms that may be specifically

linked to diabetes, its complications, and/or management. Among these factors, current therapies, peripheral neuropathy, reduced vision (caused by peripheral retinopathy and cataracts), hypoglycaemia, decreased muscle performance, diabetic foot, orthostatic hypotension, polyuria and nocturia, causing falls especially at night, reduction of reflexes, stroke, and cognitive impairment may all play an important role [19, 20]. Moreover, diabetes is associated with a delay in the wound healing [21], altered biochemical properties, and a reduction of cell proliferation and of collagen content in bone callus [22].

Paradoxically, patients with T2DM often have a normal or high BMD, probably associated with obesity as well as with hyperinsulinemia, altered level of estrogen, and/or adipokines. Despite this evidence, the risk of fractures in T2DM patients is higher and this finding could be related to the altered bone quality that does not emerge from measurements of BMD. Thus, diabetes can interfere with bone tissue causing impaired bone quality through different mechanisms [23], including glycosuria which may result in hypercalciuria and loss of bone mass; accumulation of the advanced glycosylation end products (AGEs) in the collagen fibers with alteration of the structure and of the strength of the bone; low levels of insulin like growth factors-I (IGF-I) considered as a bone anabolic factor; alteration in plasma insulin levels; impaired kidney function; bone microangiopathy with reduction of vascular flow and increased bone fragility and chronic inflammation with increase of cytokines that can accelerate the bone remodeling and loss of BMD. Further metabolic alterations could contribute to the increase of fracture risk in T2DM. Among these, high levels of homocysteine (tHcy) have been proposed as a risk factor for bone alteration and fracture risk also in postmenopausal women [24], and it has been demonstrated that tHcy levels increase after menopause in T2DM women as in not diabetic ones [25]. High tHcy levels may also indirectly influence fracture risk in T2DM, by increasing the incidence of micro- and macroangiopathy, although these associations remain to date still controversial [26, 27].

As for diabetes-specific mechanisms, several data indicate an effect of AGEs on collagen and bone cells. It was demonstrated that AGEs accumulating in the collagen stimulate IL-6 production in human bone cells [28], inhibit the phenotypic expression of osteoblasts and their differentiation and mineralization, inhibit type 1 collagen synthesis, and favor the formation of weak bridges between the collagen fibers resulting in the reduction of bone strength and in the increase of bone resorption induced by osteoclasts [29, 30]. These observations are corroborated by the presence of AGEs receptors (RAGEs) on bone cells [31]. A negative correlation between the serum levels of osteocalcin, a protein secreted by osteoblasts, and plasma glucose, fat mass and atherosclerosis in patients with T2DM was also observed [22]. Osteocalcin's function is peculiar since this protein exerts its effects not only on bone, but also on glucose and fat metabolism, working like a hormone able to regulate gene expression of β-pancreatic cells and of adipocytes and preventing the development of metabolic disease, obesity, and hyperglycaemia [32]. Furthermore, adiponectin, an adipose-tissue derived hormone, was shown to induce the proliferation, differentiation, and mineralization of osteoblasts [33].

Also altered IGF-1 levels have been associated with bone abnormalities. IGF-I is also synthesized by osteoblasts and it is a regulator of bone cells metabolism [34]. Several studies showed a reduced IGF-1 activity when glucose and AGEs levels are high, suggesting an osteoblastic resistance to IGF-1 effects [35, 36]. Kanazawa et al. showed an inverse relationship between IGF-I levels and vertebral fractures in postmenopausal T2DM women, suggesting a protective role of IGF-1 related to its effects on bone quality [37].

Also chronic inflammation may be a link between bone abnormalities and fracture risk in diabetes [38]. Inflammation induced by obesity inhibits the synthesis and secretion of adiponectin from adipose tissue, which may in turn have consequences on bone metabolism.

Among the mechanisms linking bone metabolism to T2DM, vitamin D deficiency has been extensively treated by other authors [39] and certainly merits a specific dissertation that goes beyond the aims of this review.

The relationship between the metabolic control in T2DM and bone metabolism has been the topic of numerous experimental and epidemiological studies. The results are often controversial, being influenced by the number of patients included, the study design, or the measures of glucose control. Hyperglycaemia has been shown to have a negative effect on the expression and secretion of osteocalcin by osteoblasts, and hypoglycaemic therapies can improve the levels of osteocalcin in patients with T2DM [40]. However, the Health, Aging and Body Composition Study [11] showed that T2DM patients with and without fractures had similar glycaemic control. Strotmeyer et al. [41] found no significant correlation between HbA1c levels, BMD, and bone volume, but they showed a negative correlation between the duration of the disease and hip BMD, with the hip BMD mean values progressively decreasing from the cases with a recent diagnosis of diabetes, to those with more than 20 years of diabetes, every 5–10 years' intervals. On the other hand, other studies observed an improvement and a stabilization in BMD in patients with T1DM in good metabolic control [42, 43]. Another study, aimed at evaluating the causes of low bone quality in diabetic subjects, identified low PTH levels accompanied by low bone formation as a potential contributor to the high vertebral fracture risk independently of bone mineral density risk in T2DM postmenopausal women [44].

All these experimental evidences support the pathogenic role of insulin-resistance, chronic inflammation, and long-term diabetes-specific factors, such as the formation of AGEs on the alterations of bone structure, that are at the basis of the increased fracture risk in T2DM patients. More controversial is the role of glucose control on bone mass measures, such as BMD.

To date, no gender-specific differences have been reported in these pathogenic mechanisms, although an already fragile bone such as that observed in postmenopausal women due to hormonal loss may certainly play a role in accelerating bone structure disruption.

4. Bone Mass versus Bone Quality in Type 2 Diabetes

The first data evaluating osteoporosis in T2DM showed high BMD values when compared to nondiabetic controls [22]. However, a subsequent meta-analysis showed that patients with T2DM had a higher risk of fractures in spite of this higher BMD, highlighting the discrepancies between BMD and fracture risk and suggesting that measuring BMD may not reflect bone fragility of these patients [45].

Gorman et al. [46] assessed bone status in older adults with and without T2DM through a literature review. Some of these studies were not limited to the use of DXA but used more recent techniques, such as quantitative computed tomography (QCT) [47], the peripheral quantitative computed tomography (pQCT) [48], and quantitative ultrasound (QUS) [49, 50], that allow distinguishing the bone compartments (cortical and trabecular), assessing bone quality (microarchitecture and geometry), and estimating bone strength. Results obtained with the use of DXA were consistent with previous studies, showing an equal or higher BMD among older adults with diabetes compared with controls [31]; conversely, those studies using the QCT and pQCT [47–50] suggested the presence of profound changes in bone geometry in diabetic subjects, potentially explaining the increased risk of fractures observed in these patients. In addition, phalangeal quantitative ultrasound (QUS) has been increasingly used for its ease of use and because it may be more helpful than DXA in detecting bone deficits, also in diabetic subjects [49, 51]. Recently, the use of DXA based trabecular bone score has been proposed as a new complementary approach to ameliorate fracture risk prediction in T2DM [52].

All these evidences suggest that the DXA alone is not able to predict the risk of fractures in older adults with diabetes, where bone health may depend upon too many factors, including BMI. At this regard, Shan et al. [53] observed that T2DM patients with a greater BMD were those with greater BMI, suggesting that BMD measures may be overestimated in obese subjects.

Since the measurement of BMD is not capable of predicting the risk of fractures among people with T2DM, it is necessary to have valid instruments to determine, in the clinical practice, not only fracture risk but also the most appropriate time to start a proper therapy. In a large study of postmenopausal women there was a greater chance of new fracture (vertebral or even) among those who had already had a vertebral fracture; the authors highlighted the possible use of prior vertebral fractures as an indicator of bone quality in these patients [54]. Furthermore, Yamamoto et al. observed radiographic vertebral fractures in 38% of T2DM males and 31% of T2DM females, with a 16% of the subjects having a personal history of previous fractures, and concluded that simple procedures such as medical history and X-ray can be used in clinical practice for the assessment of fracture risk in the diabetic population [55].

Among the different tools to assess fracture risk, the WHO fracture risk assessment (FRAX) is a computer-based algorithm (http://www.shef.ac.uk/FRAX/) primarily intended for use in primary care [56, 57]. FRAX calculates fracture probability from easily obtained clinical risk factors: age, sex, BMI, prolonged use of glucocorticoids, current smoking, alcohol intake of three or more units per day, a parental history of hip fracture, secondary osteoporosis, rheumatoid arthritis, prior fragility fracture, and (optionally) femoral neck BMD or T-score. The output, which estimates probabilities for major osteoporotic fracture (hip, clinical spine, humerus, or forearm) and hip fracture over 10 years, has been shown to improve fracture prediction over T-score alone [58]. Although T2DM is not a primary entry variable in the current FRAX construction, T1D is considered in FRAX as one of the secondary causes of osteoporosis, increasing the calculated fracture probability when BMD is not known. Furthermore, two recent reports have shown that, for a given FRAX probability or T-score and age, the risk of fracture among individuals with diabetes is higher than the risk in nondiabetics [59, 60]. In another study, mean FRAX hip fracture and FRAX major osteoporotic fracture were significantly higher in the T2DM cohort as compared to the healthy age-matched males [61, 62].

To date few studies specifically addressed potential gender differences in BMD measures in T2DM. One of the first studies by Barrett-Connor and Holbrook [63] evaluated the association of T2DM with BMD in men and women, separately. Men with diabetes had BMD levels similar to those with normal glucose tolerance, whereas women with diabetes had significantly higher BMD levels at all sites than control women, and these differences were unexplained by several potential confounders such as age, obesity, cigarette smoking, alcohol intake, regular physical activity, and the use of diuretics and estrogen. The authors related these diabetes-related differences to the greater androgenicity reported in hyperinsulinemic T2DM women. These results were confirmed in another study showing that diabetic men had a BMD similar to that of the control group, whereas diabetic women had a higher BMD than controls, showing a positive relationship between BMD and triglycerides and a negative relationship with HDL-C only in women [64]. A recent study evaluating bone metabolism by measuring markers of bone turnover and BMD, taking into account the presence of diabetic polyneuropathy (PNP), showed that male diabetic patients with PNP had a higher rate of bone turnover than men without PNP, indicating neuropathy as a potential risk factor for osteoporosis and fracture risk, beyond the risk associated with falls [65]. Finally, in a large population of men and women undergoing hip DXA, including 2929 women and 460 men with known diabetes, women had significantly lower mean spine-hip thickness differences than men (3.3 ± 1.4 cm versus 5.4 ± 1.7 cm; $p < 0.001$), which persisted after adjustment for sex-specific differences of age and BMI. Logistic regression showed that a greater spine-hip thickness difference was significantly associated with higher likelihood of having diabetes even after adjustment for age and BMI, and this effect was stronger among women than among men [66].

Despite the higher BMD found in T2DM subjects, fracture risk remains high in these patients, suggesting that BMD alone does not reflect the profound rearrangement of bone structure associated with metabolic disease. This knowledge

has led some authors to introduce the term of "diabetic osteodystrophy" [67] and to search other methods to assess bone quality in T2DM patients. When specifically addressing gender differences in this issue, the few available studies that have evaluated separately men and women with diabetes relied on BMD measures, and most of them indicated high BMD values in T2DM women but not in men, when compared to control population. Studies using other markers of bone quality in T2DM are urgently needed to establish whether the higher fracture risk observed in T2DM is only related to the risk of falls associated to diabetes management and/or long-term complications, or more likely to specific alterations in bone metabolism, and finally whether all these factors differently affect T2DM men and women.

5. Effects of Hypoglycaemic Drugs on Bone Metabolism and Fracture Risk

Hypoglycaemic drugs may also affect bone metabolism and influence fracture risk in many ways, including the increase of bone turnover and skeletal fragility, the loss of the anabolic effects of insulin in insulin-resistant states, and by augmenting the risk of falling due to hypoglycaemic episodes [68].

5.1. Insulin Therapy. It is well known that insulin exerts anabolic effects on bone, which include the regulation of bone cells proliferation and apoptosis, and the synthesis of collagen [22], probably through direct receptor-mediated effects since insulin receptors were identified on osteoblasts and their precursors. However, insulin treatment is associated with a higher rate of falls and with an increased fracture risk, both in men and in women [69, 70]. This higher risk could also reflect the fact that insulin therapy is usually employed in T2DM patients with a longer diabetes duration, when multiple chronic complications and comorbidities are common [71]. Moreover, hypoglycaemic episodes are a major complication of the treatment with insulin and may imply a high rate of falls in insulin-treated subjects. Accordingly, Kennedy et al. observed that insulin-treated subjects were more likely to fall and to have bone fracture as a consequence of the fall, during a hypoglycaemic episode as compared to non-insulin-treated patients [72].

5.2. Metformin. Available data suggest that metformin has positive effects on bone metabolism. *In vitro* and animal studies indicated that metformin inhibits adipocyte differentiation and stimulates osteoblasts' differentiation, through the inhibition of PPAR gamma [73] and the transactivation of osteoblast-specific Runx2 transcription factor [74]. Moreover, the drug also stimulates osteoblastic expression of osteoprotegerin and depresses that of RANKL, which in turn inhibits osteoclast function and bone loss [75]. Notably, RANKL has been recently proposed as a predictor of incident T2DM, and its blockade resulted in significant improvements of glucose tolerance [76, 77].

Metformin could also play a protective role on osteoblasts, by limiting the detrimental effects of AGEs. These mechanisms could account for the reduced fracture risk observed in metformin-treated patients, despite the decrease of insulin plasma levels [78]. When considering fracture risk in these patients it is however important to keep in mind that metformin is usually prescribed in younger subjects with lower complications and comorbidities rates, who also may present a lower risk of bone fracture.

Furthermore, the potential protective effect of metformin on bone and fractures risk, suggested in animal models [73, 74], was not confirmed in clinical studies [78].

For this and other reasons, including the paucity of clinical data, the protective role of metformin on bone is still debated [70].

5.3. Sulfonylureas. Sparse results suggest a protective effect of sulfonylureas on fracture risk [79]. However, hypoglycaemia is a common adverse effect of the treatment with this class of drugs. A recent review evaluating the risk of fall-related fracture in T2DM subjects on sulfonylureas concluded that available studies suffer methodological limitations and may have underestimated the risk [80, 81]. Further studies are needed to define the effect of these drugs on falls and fractures, although the overall beneficial effects of this class of drugs are currently debated [34, 82].

5.4. Thiazolidinediones. Thiazolidinediones have been shown to exert detrimental effects on the skeleton [83]. These insulin-sensitizing agents significantly increase the incidence of bone fracture, at least in T2DM postmenopausal women, whereas less conclusive results were obtained in men. The ADOPT (A Diabetes Outcome Progression Testing) study, comparing rosiglitazone with metformin and glyburide monotherapy in patients with recently diagnosed T2DM, showed a two-fold increased incidence of bone fractures in women treated with rosiglitazone in comparison with other treatment groups [84]. Interestingly, no difference in bone fractures was found in men. The increased bone fractures risk in rosiglitazone-treated group was observed both in postmenopausal and in premenopausal women and did not appear to be modified by estrogen use. The site of fractures was atypical compared with those related to postmenopausal osteoporosis (hip and spine), with more frequent fractures observed in upper and lower limbs (proximal humerus RR > 8; hand RR $= 2.6$; foot RR $= 3.3$). However these data may be related to the age of the population (<65 years) in which the rate of hip and spine fractures is relatively low. *Post-hoc* analyses showed that the increase in fracture risk was evident after about one year of treatment [85]. An increased fracture risk was observed also in women, but not in men, treated with pioglitazone, as reported in a letter to health care providers by Takeda Pharmaceuticals, IL, USA, the manufacturer of pioglitazone [86]. Clinical trials testing the short-term effects of rosiglitazone and pioglitazone on markers of bone formation in different populations suggest that, in women, thiazolidinediones cause a more rapid bone loss. In particular, modifications in bone turnover markers indicate a pattern of reduced bone formation without a change in resorption [87–89]. Thiazolidinediones ameliorate insulin sensitivity of muscle and adipose tissue, by acting

as agonists of peroxisome proliferator-activated receptor-gamma (PPAR gamma). Via the same mechanism, however, they promote an imbalance in bone remodeling and changes in bone marrow structure and function. The bone loss may result from the preferential differentiation of mesenchymal stem cells into adipocytes rather than osteoblasts, and the increase of osteoclast activity [90]. These data are consistent with two observational clinical trials demonstrating bone loss in T2DM subjects treated with rosiglitazone and pioglitazone, an effect that seems to correlate with the duration of treatment [91, 92].

5.5. Incretin-Based Therapies. In addition to their beneficial effects on glucose metabolism and cardiovascular risk factors [93], several data indicate that incretin-based drugs, that is, glucagon like peptide-1 receptor agonists (GLP-1-RAs) and inhibitors of the dipeptidyl peptidase-4 enzyme (DPP-4), may positively affect bone metabolism.

Bone cells, including osteoblasts and osteoclasts, express receptors for GLP-1 and data from animal studies suggest that incretins play a regulatory role in bone turnover, in response to ingestion of nutrients. This regulatory activity results in increased bone formation and reduced bone resorption in times of energy sufficiency. In particular, GLP-1 inhibits bone resorption through a calcitonin-dependent way [94]. Also the favorable effects of GLP-1RAs on body weight may influence bone metabolism; however exenatide twice daily did not affect BMD and markers of bone homeostasis in T2DM subjects, as compared to insulin glargine, despite body weight reduction [95].

Notably, incretin-based therapy is also associated with a low hypoglycaemic risk, and it may potentially reduce the fall-related fractures in T2DM subjects. However, clinical data available to date are too limited and not conclusive yet. Recently, a meta-analysis investigated the association of treatment with the GLP-1RAs exenatide and liraglutide with bone fractures incidence in T2DM subjects, showing no effects on fracture risk, as compared to placebo or other antidiabetic drugs (glimepiride, sitagliptin, and insulin) [96]. Conversely, another recent meta-analysis showed an increased risk of bone fractures in subjects treated with exenatide but a reduced risk of nonvertebral fractures with liraglutide, as compared to other medications [97]. However, it is important to point that all the studies included in both meta-analyses were not specifically designed to evaluate fracture risk.

As for the effects of DPP-4 inhibitors on bone metabolism, no difference in bone fracture risk was observed between T2DM subjects treated with these drugs and non-diabetic controls, in a retrospective study using data from the Clinical Practice Research Datalink [98]. Conversely, a meta-analysis of 28 relatively short-term studies suggested that therapy with DPP-4 inhibitors is associated with a significant reduction in fracture risk, as compared to placebo or other antidiabetic agents [99].

5.6. Sodium Glucose Cotransporter 2 Inhibitors. Sodium glucose cotransporter 2 (SGLT2) inhibitors reduce glucose plasma levels by inhibiting proximal tubular reabsorption of glucose in the kidney. In addition to their demonstrated glycaemic efficacy, these drugs provide several clinical benefits, including body weight loss, the reduction of blood pressure values, and the low risk of hypoglycaemic events. Clinical data suggest that treatment with SGLT2 is associated with an increased risk of bone fractures. Because of their mechanism of action these drugs may influence calcium-phosphate homeostasis and potentially have an effect on bone metabolism and turnover. Several mechanisms may be involved: the raise of serum phosphate levels via increased tubular resorption of phosphate in the kidney; the increase of magnesium and PTH levels; the reduction of 25OH-vitamin D levels; and the increase of secretion of FGF23 by osteocytes; also weight loss frequently observed with SGLT2 may influence bone mass [100]. Serum phosphate, magnesium, and PTH levels are increased in subjects treated with dapagliflozin, as compared to those on placebo [101, 102]; however Ljunggren et al., in spite of a small increase in serum phosphate and magnesium levels, did not observe any changes from baseline in bone turnover markers or BMD after 50 weeks' treatment with dapagliflozin 10 mg/day versus placebo [101]. Furthermore, no risk of bone fracture associated with dapagliflozin emerged in a pooled analysis using data from 12 placebo-controlled studies [103]. Conversely, in a population of 252 T2DM subjects with moderate renal impairment treated with dapagliflozin or placebo for 104 weeks, low-trauma fractures were observed in 6% and 9.4% of patients on dapagliflozin 5 and 10 mg, respectively, whereas no bone fractures were reported in the placebo group [102].

Data on empagliflozin available to date do not show an increased risk of bone fracture or an impairment in BMD, compared to placebo [104].

Recently, a pooled analysis of nine clinical trials has shown that the use of canagliflozin is associated with an increased fracture incidence, particularly in women [105]. Furthermore a recent postmarketing safety study required by the Food and Drug Administration (FDA) showed a significant reduction in BMD at the lumbar spine and the hip, as detected by DXA, after 52 weeks of therapy with canagliflozin in a population of >700 elderly subjects [106]. Notably, the FDA has strengthened the warning for the increased risk of bone fractures with canagliflozin and invited health care professionals to consider factors that may contribute to this risk prior to starting treatment. The FDA revised the canagliflozin label and it is evaluating the risk of bone fractures with dapagliflozin and empagliflozin to determine if additional label changes or studies are needed. However effects of SGLT2 on bone fracture risk are not fully elucidated yet and further studies are needed to better clarify this issue. In particular it remains unclear if the effect on bone metabolism is a drug class-effect or there are differences between different molecules of the class, which may be sustained by differences in the degree of inhibition of renal cotransporter SGLT2 at maximum dosage, which is stronger for canagliflozin 300 mg than for dapagliflozin 10 mg.

6. Conclusions

Aging is associated with increasing prevalence of both diabetes and osteoporosis and these chronic diseases are frequently associated in the elderly, especially in women.

Although osteoporosis and T2DM seem to be unrelated from a pathophysiological standpoint, a number of epidemiological studies have demonstrated an increased fracture risk among patients with T2DM. This higher risk is likely due to a combination of greater risk of falling, regional osteopenia, and impaired bone quality and treatment effects.

Despite the well-documented higher fracture risk in T2DM, BMD measures show higher values in these patients. This apparent discrepancy is likely explained by the lower quality of bone in T2DM subjects, as documented by modern techniques investigating bone structure and strength, which may be more suitable to assess osteoporotic risk than DXA in these patients.

Different mechanisms have been proposed to explain the possible influences of diabetes on bone metabolism, including glycosuria, AGEs, low levels of IGF-I or alteration in plasma insulin levels, impaired kidney function, and chronic inflammation.

Also factors related to diabetes complications and/or to its management such as poor metabolic control or the use of some hypoglycaemic drugs may influence osteoporosis and/or fracture risk in T2DM patients. In particular, several medications used in the treatment of T2DM may have an impact on bone metabolism, and they should be used with caution in patients who are at risk for fall and/or fracture, particularly in postmenopausal T2DM women.

Thus, when considering the effects of hypoglycaemic drugs on bone it is important to balance their potential direct effects on bone metabolism with the risk of falling-related fractures due to the associated hypoglycaemic risk. Furthermore, for drugs which are usually prescribed in long-standing diabetes, such as insulin, the inclusion of subjects with diabetes micro- and macrovascular complications, especially retinopathy and neuropathy, should be taken into account when evaluating fracture risk.

Women are typically more exposed to osteoporosis risk, and men and women differ in terms of risk factors for falls and osteoporosis [107], but to date only few epidemiological studies specifically examined osteoporosis and fracture risk in T2DM men and women separately; furthermore, direct comparisons of men and women with T2DM are lacking. Although gender-related data on bone metabolism, bone measures, and fracture risk are too sparse to drew firm conclusions, available literature indicates that, because of diabetes, men may be less protected from osteoporosis than nondiabetic counterparts, although some authors reported no differences in BMD measures compared to nondiabetic men. Data on women are even more conflicting, with studies showing a higher BMD in those with than without T2DM. The inconsistency of literature on this issue may be related to the fact that BMD measures that have been extensively used to date are not the best marker of bone health in T2DM subjects, and more differences may emerge from future studies evaluating bone turnover markers in the two genders. As for hypoglycaemic drugs, thiazolidinediones are the only ones with well-documented negative effects on bone metabolism, which shows a gender dimorphism, being more clinically relevant in women than in men. This gender difference could be related to circulating estrogen levels, since estrogens reduce adipogenesis, the apoptosis of osteocytes, and the upregulation of sclerostin, which acts by inhibiting bone formation. However bone loss has been observed both in premenopausal and in postmenopausal women, so the matter remains unresolved. Unfortunately, little is known about the impact of most diabetes treatments on bone quality and specifically on fracture risk. Besides metformin and sulphonylureas, which do not seem to have specific effects on bone, several data point to a protective role of incretin-based therapies on fracture risk. These potential beneficial effects may rise from direct GLP-1R-mediated effects on bone metabolism but also from the low hypoglycaemic risk which may be protective against falling. Data on SGLT-2 inhibitors are still too sparse to identify whether the potential detrimental effects on bone are a class-effect or they are limited to specific drugs.

T2DM prevalence increases with age, and glucose lowering therapies are often prescribed in older subjects at higher fracture risk. Notably, although osteoporosis is typically a "female disease," to date it is still largely unclear whether the bone effects of hypoglycaemic drugs are gender-specific. A better understanding of the real impact of diabetes treatments on bone quality and fracture risk is necessary to create personalized therapy, especially in subjects at higher risk, such as women and older patients.

Competing Interests

The authors declare no competing interests.

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Review Article

Gestational Diabetes Mellitus and Future Cardiovascular Risk: An Update

S. Burlina, M. G. Dalfrà, N. C. Chilelli, and A. Lapolla

Department of Medicine (DIMED), University of Padova, Via Giustiniani, No. 2, 35128 Padova, Italy

Correspondence should be addressed to A. Lapolla; annunziata.lapolla@unipd.it

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The prevalence of gestational diabetes mellitus is increasing in parallel with the rising prevalence of type 2 diabetes and obesity around the world. Current evidence strongly suggests that women who have had gestational diabetes mellitus are at greater risk of cardiovascular disease later in life. Given the growing prevalence of gestational diabetes mellitus, it is important to identify appropriate reliable markers of cardiovascular disease and specific treatment strategies capable of containing obesity, diabetes, and metabolic syndrome in order to reduce the burden of cardiovascular disease in the women affected.

1. Introduction

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance developing or first recognized during pregnancy that is not clearly overt diabetes. It affects from 5-6% to 15–20% of pregnancies worldwide, depending on population demographics, screening methods, diagnostic criteria in use, and maternal lifestyle [1]. The pathophysiological mechanisms behind the onset of GDM are still not well understood. In the second and third trimesters of pregnancy, there is a physiological increase of insulin resistance as a result of placental hormones such as estrogen, progesterone, human placental lactogen, human placenta growth hormone, and cortisol that antagonize the action of insulin [2]. The gradual decline in insulin sensitivity is considered a physiological mechanism that helps to provide glucose to the fetus, and it coincides with a gradual increase in the secretion of insulin to maintain normal glucose tolerance [3, 4]. Pregnancy is *per se* a hyperinsulinemic condition and GDM may develop if insulin secretion by the beta cells is unable to compensate the pregnancy-associated insulin resistance [5]. Most women with GDM are overweight or obese and have all the features of metabolic syndrome, but lean women with none of the common risk factors can develop GDM too.

Women with GDM are at greater risk of metabolic syndrome (characterized by central obesity, dyslipidemia, and insulin resistance) and type 2 diabetes years after their pregnancy [6, 7]. GDM progresses to type 2 diabetes in the years after pregnancy with a cumulative incidence in the range of 2.6–70%, from 6 weeks to 28 years postpartum [7].

Women who develop GDM are also at higher risk of overt cardiovascular disease (CVD) later in life [8]. While a diagnosis of type 2 diabetes in these women markedly raises their CVD risk [8], some studies have demonstrated that a diagnosis of GDM alone contributes to this risk, with or without any subsequent type 2 diabetes. In a cross-sectional study, 332 women with a history of GDM had a higher prevalence of CVD 29.9 years after the index pregnancy (adjusted OR: 1.85; 95% CI: 1.21–2.82), irrespective of any type 2 diabetes (OR: 1.56; 95% CI: 1.002–2.43) [8]. Retnakaran and Shah investigated the possible relationship between mild glucose tolerance in pregnancy and CVD risk in later life in a retrospective population-based cohort study [9]. They studied 13,888 women who developed GDM, 71,831 women who had an abnormal 50 g glucose test result but no GDM, and 349,977 women who had a normal response to the 50 g glucose challenge, with a median follow-up of 12.3 years. Compared with the women with normal glucose tolerance, the authors found an adjusted hazard ratio for CVD (acute myocardial infarction, coronary bypass, coronary angioplasty, stroke, and carotid endarterectomy) of 1.66 (95% CI: 1.30–2.13) for the GDM women and 1.19 (95% CI: 1.02–1.39) for the women with an abnormal glucose test result. Adjusting for the subsequent onset of type 2 diabetes led to attenuation of the hazard ratios

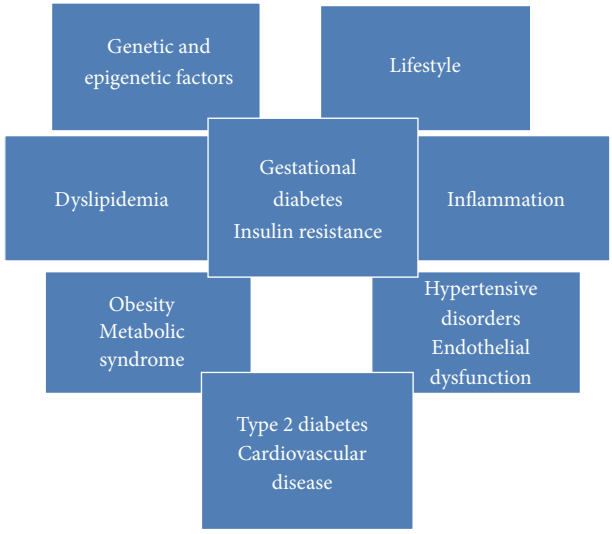

Figure 1: Relationship between GDM and subsequent cardiovascular disease: modifiable and unmodifiable risk factors.

for CVD, which became 1.25 (95% CI: 0.96–1.62) for the GDM group and 1.16 (95% CI: 0.99–1.36) for the group with an abnormal glucose test result. The authors concluded that even women with mild hyperglycemia in pregnancy, but no GDM, are at higher risk of subsequent adverse cardiovascular outcomes. It should be emphasized, however, that a large proportion of the elevated CVD risk in the abovementioned study could relate to the subsequent onset of type 2 diabetes, as suggested by the hazard ratios adjusted for this diagnosis.

Be that as it may, the effect of GDM on the risk of CVD remains to be fully elucidated: it is still not clear whether the association existing between GDM and CVD is independent of the increased risk of CVD associated with type 2 diabetes.

In this paper, we review the relationship between common CVD risk factors and a history of GDM and take a look at potential new markers of CVD in such women (Figure 1).

2. Methods

A review of the international literature was conducted as regards the cardiovascular risk for women with GDM or a history of GDM. The keywords used were as follows: gestational diabetes mellitus, cardiovascular disease, cardiovascular risk, vascular disease, pregnancy, and pregnancy complication. Only data deriving from human studies and produced from 2005 onwards were considered in order to ensure that the evidence was topical. Literature dating from before 2005 was only included if it was particularly relevant. Data regarding patients with prior diabetes (type 1 or type 2) were not considered.

3. Common CVD Risk Factors in Women with a History of GDM

3.1. Hypertension. In the literature, there is plenty of evidence of a greater risk of hypertension in women with a history of GDM. Carr et al. [8] demonstrated that women with prior GDM were more likely to develop hypertension than women with no history of GDM (46.8% versus 37%; $p < 0.001$) and that any hypertension would be diagnosed at an earlier age in the former than in the latter (40 ± 1.0 versus 47.8 ± 0.9 years; $p < 0.001$). Kaul et al. [16] studied a large cohort of 240,083 women giving birth over a 10-year period. During this time, 14.9% of the nonobese women with a history of GDM developed hypertension; the hazard ratio, adjusted for maternal age, preeclampsia, parity, smoking status, ethnicity, and socioeconomic status, was 2.0 (1.8–2.2); and in the obese women with a history of GDM, the rate of hypertension rose to 26.8% and the hazard ratio to 3.7 (3.2–4.3). Goueslard et al. [17] recently reported on a large nationwide population-based retrospective study conducted in France, with a follow-up of 7 years. They considered 62,958 women with and 1,452,429 women without a history of GDM. The results of logistic regression analysis adjusted for age showed that GDM was associated with a significantly higher risk of hypertension, with an adjusted OR of 2.92 (2.77–3.08).

3.2. Dyslipidemia. Numerous published reports demonstrate that women with a history of GDM are more dyslipidemic. Like the situation seen for hypertension, Carr et al. showed that women who developed GDM were more likely to report a history of acquired dyslipidemia (33.9% versus 26.3%; $p < 0.05$), to take medication for dyslipidemia (18.4% versus 13.7%; $p < 0.05$), and to be diagnosed with dyslipidemia at a younger age (47.6 ± 1.3 versus 51.9 ± 1.0 years; $p = 0.01$) than women with no history of GDM [8]. In another study [18], women with singleton pregnancies who had GDM or normal glucose tolerance were examined from 2 to 24 months after their pregnancy: those with a history of GDM had higher total cholesterol (5.06 versus 4.56 mmol/L; $p = 0.001$), LDL-cholesterol (3.17 versus 2.57 mmol/L; $p = 0.001$), and triglyceride levels (1.02 versus 0.86 mmol/L; $p = 0.01$) and lower HDL-cholesterol levels (1.53 versus 1.73 mmol/L; $p = 0.001$). In a similar study population, Retnakaran et al. found GDM to be an independent predictor of total cholesterol, LDL-cholesterol, and triglyceride levels measured 3 months after delivery. These authors also demonstrated a stronger correlation between the area under the curve on the antepartum oral glucose tolerance test and postpartum levels of LDL-cholesterol and triglycerides, total cholesterol to HDL ratio, apoB, and apoB to apoA1 ratio (all $r > 0.21$; $p < 0.0001$) and an inverse relationship with HDL-cholesterol ($r = -0.21$; $p < 0.0001$), after adjusting for age, ethnicity, and family history of diabetes [19].

3.3. Metabolic Syndrome (Table 1). Metabolic syndrome is characterized by abdominal obesity, hypertension, dyslipidemia, and abnormal glucose tolerance [20]. The condition carries a six- to eightfold higher risk of CVD and a two- to threefold higher CVD-related mortality rate by comparison with healthy controls [21].

Women who have had GDM are at high risk of developing metabolic syndrome. In a cohort of Caucasian women, for instance, the prevalence of metabolic syndrome 16 months after delivery was 9% among the women with a history of

Table 1: Frequency of metabolic syndromes in women with a history of gestational diabetes mellitus, according to the literature.

Authors	Follow-up	Prevalence of metabolic syndrome (%)	Diagnostic criteria for metabolic syndrome
Bo et al., 2004 [10]	8.5 yrs	21	ATP III
Albareda et al., 2005 [11]	5 yrs	11.1	ATP III
Lauenborg et al., 2005 [12]	9.8 yrs	38.4	WHO
Di Cianni et al., 2007 [13]	16 months	9	ATP III
Vilmi-Kerälä et al., 2015 [14]	2–6 yrs	23.1	ATP III
Noctor et al., 2015 [15]	2.6 yrs	25.3	WHO

GDM and only 1% among controls ($p < 0.01$), when NCEP, ATP III criteria were applied [13]. This prevalence rose from 9% to 14.5% for the former and from 1% to 2% for the latter when IDF criteria were adopted ($p < 0.001$) [22]. Other studies on cohorts of Caucasian women with a follow-up ranging from 5 to 11 years after delivery found that the prevalence of metabolic syndrome among the women with a history of GDM ranged from 11.1% to 43%, as opposed to 4.6–6.1% in a control population [10–12]. A recent hospital-based cohort study found that the risk of metabolic syndrome 2–6 years after delivery was 2.4 times higher in women with a history of GDM than in those with normal glucose tolerance in pregnancy. Multivariate analysis indicated that a history of GDM predicted the onset of metabolic syndrome with an OR of 2.83 [14]. Noctor et al. [15] recently examined the prevalence of metabolic syndrome in women with a history of GDM according to the new criteria for the diagnosis of this condition [23]. Their sample consisted of 265 women with a history of GDM at a mean of 2.6 years after the index pregnancy and 378 women with normal glucose tolerance in pregnancy at a mean of 3.3 years after pregnancy. According to the ATP III criteria, 25.3% of the GDM women had metabolic syndrome as opposed to 6.6% of the controls. The authors also found that obesity confers a significant excess risk of metabolic syndrome in women who have had GDM, with an OR of 3.9 (95% CI: 2.0–7.9) for obese women with as opposed to without a history of GDM.

4. Early Changes in Vascular Structure and Function in Women with a History of GDM

Even women with a history of GDM who have no common CV risk factors are at greater risk of CVD than those with normal glucose tolerance in pregnancy. GDM seems to have a significant impact on endothelial function and structure, triggering the first step towards the development of atherosclerosis.

Carotid artery intima-media thickness (cIMT) is a subclinical measure of early atherosclerosis that strongly predicts heart disease and stroke, particularly in women [24]. In recent years, numerous studies have been published on cIMT in women who have had GDM. Bo et al. measured cIMT six and a half years after delivery in 82 women with and 113 without a history of GDM [25]. They found cIMT to be significantly higher in the former than in the latter, even among women with no components of metabolic syndrome, and irrespective of their BMI. cIMT was also significantly associated with a history of GDM in a multiple regression analysis, after adjusting for waist circumference, BMI, blood pressure, and blood glucose levels. Volpe et al. investigated cIMT two years after delivery in 28 women with and 24 without a history of GDM [26]. There were no differences between the two groups in terms of BMI, but the cIMT values were higher in the GDM women, though they were still within the upper limit of normal (0.57 ± 0.058 versus 0.51 ± 0.051 mm, $p < 0.01$). It is important to mention, however, that these groups also differed in terms of the principal components of metabolic syndrome (waist circumference, blood pressure, fasting plasma glucose, and triglycerides), which were all significantly higher in the GDM women than in the controls. In a population-based, multicenter, longitudinal, and observational study conducted by Gunderson et al. [27], 898 women with no diabetes or heart disease at the baseline subsequently had >1 delivery and then reported their GDM history and underwent cIMT measurement 20 years later. Among the women who developed no type 2 diabetes or metabolic syndrome during the 20-year follow-up, the mean cIMT was 0.023 mm greater for the women with a history of GDM in a model adjusted for age, race, parity, and prepregnancy BMI. On the other hand, the mean cIMT did not differ by GDM history among the women who developed type 2 diabetes or metabolic syndrome during the follow-up. The authors concluded that a history of GDM can be considered a risk factor for atherosclerosis even before the onset of diabetes or metabolic syndrome.

Another proposed surrogate marker for the early detection of atherosclerosis is the flow-mediated dilation (FMD) of the brachial artery [28], which is an indicator of endothelial dysfunction—one of the earliest signs of atherosclerosis [29]. Anastasiou et al. measured FMD 3–6 months after delivery in nonobese and obese women with a history of GDM [30]. They found FMD to be significantly lower in both nonobese and obese GDM women than in control women. They also showed that FMD correlated inversely with BMI, serum total cholesterol, and basal insulin resistance (assessed with a homeostasis model). Davenport et al. found FMD to be impaired in GDM women already 7–9 weeks after delivery. In this particular study, a sample of women was divided into 4 groups: those with a history of GDM who had become normoglycemic; those with a history of GDM who remained hyperglycemic; those with no history of GDM; and those who had never been pregnant. FMD was significantly lower in the former two groups than in the latter two. Interestingly, FMD no longer differed significantly between the four groups after controlling for glucose AUC, which goes to show the

importance of postpartum hyperglycemia in determining endothelial dysfunction after pregnancy [31]. After adjusting for age and blood pressure levels, Fakhrzadeh et al. reported a significant reduction in FMD 4 years after delivery in women with a history of GDM [32] by comparison with control women ($26 \pm 0.11\%$ versus $19.32 \pm 0.05\%$; $p = 0.003$). They also reported finding no correlation between FMD and inflammatory parameters, lipid profile, or insulin resistance indices; they did not consider glucose AUC.

Hannemann et al., on the other hand, found no differences in FMD between women who had experienced GDM five years earlier and control women matched for age, BMI, and smoking habits [33]. Brewster et al. likewise found no differences in FMD between women with a history of GDM and control women 6 years after delivery (mean 8.5% versus 9.3%, $p = 0.61$) [34]. There is therefore no way of saying for sure that FMD is impaired in later years in women who have had GDM. It is worth noting that most of the studies that did find a worse FMD were conducted soon after delivery, so it may be that this impairment is an early vascular function abnormality that may return to normal with time if glucose tolerance returns to normal; that is, FMD could be influenced mainly by hyperglycemia. Supporting this hypothesis, two studies have demonstrated that FMD is reduced during pregnancy in women with GDM. Paradisi et al. found FMD to be significantly lower in GDM women than in controls ($4.1 \pm 0.9\%$ versus $10.9 \pm 1.1\%$; $p < 0.0001$) in the third trimester of pregnancy [35]. They found too that glucose AUC independently influenced FMD ($p < 0.0001$). In another cross-sectional study on pregnant women with GDM (n. 19) or preeclampsia (n. 42) and controls with normal glucose tolerance and blood pressure (n. 19), Guimarães et al. also demonstrated a significantly reduced FMD in the women with GDM or preeclampsia by comparison with the controls, and they suggested the possibility of endothelial injury in such patients [36].

In this setting, Caliskan et al. recently studied the coronary flow velocity reserve (CFVR), which reflects coronary microvascular function, in women with a history of GDM 6 months after delivery. They found this parameter to be significantly reduced in the GDM women by comparison with controls whose glucose tolerance remained normal in pregnancy (2.34 ± 0.39 versus 2.83 ± 0.21; $p < 0.001$) and also that insulin resistance, hyperglycemia, and oxidative stress markers were negatively associated with CVFR. On multivariate analysis, the authors also found an independent association between CFVR and GDM ($p = 0.02$) [37].

5. New Markers

Endothelial dysfunction is believed to be an important initiating factor in the development of atherosclerosis [29]. Like circulating levels of systemic inflammatory markers, the levels of some adipokines have also been associated with endothelial dysfunction and atherosclerosis. Apelin, a recently discovered adipocytokine, is an endogenous ligand of the G protein-coupled receptor APJ [38] that is produced by adipose tissue and expressed in various tissues (brain, lung, heart, pancreas, kidney, and endothelial cells) and believed to have a role in the cardiovascular system [39].

In a recent study, 141 women with a history of GDM and 49 age- and BMI-matched healthy control women were tested for circulating apelin, IL-6, and plasminogen activator inhibitor levels and IMT and took an oral glucose tolerance challenge. The results showed that plasma apelin levels were lower in women with a history of GDM and, in multiple regression analysis, they were negatively associated with fasting and postload glucose, IL-6, and carotid IMT. Suppressed apelin levels are therefore associated with a higher cardiovascular risk in women with a history of GDM [40].

Subclinical inflammation is another major risk factor for future CVD in the general population, and the higher risk of CVD later in life for women with a history of GDM is potentially at least partly due to inflammatory mechanisms [13]. Although several studies have demonstrated higher levels of markers reflecting vascular inflammation in women who have had GDM, the mechanisms behind vascular injury and CVD are not well understood [13].

Osteoprotegerin (OPG) is a soluble member of the tumor necrosis factor (TNF) receptor superfamily that inhibits osteoclast maturation and protects bone from normal osteoclast remodeling [41]. OPG has an important role in lymphocyte development and apoptosis too, and its levels have been associated with CVD [42]. In a cross-sectional case-control study, 128 women with a history of GDM and 67 age-matched controls were considered for a diagnosis of metabolic syndrome according to the criteria of the American Heart Association (AHA), and their glucose and insulin levels, serum lipids, OPG, and cIMT were also measured. The women who were confirmed to have metabolic syndrome had higher OPG levels than those who were not, or healthy controls; and serum OPG levels were found to be associated with obesity, insulin resistance, and cIMT [43].

Pentraxin 3 (PTX3) is an essential component of innate immunity induced by various inflammatory stimuli. It is produced by endothelial cell macrophages and granulocytes at sites of inflammation [44] and may have a cardioprotective role: higher levels in patients with CVD reflect a beneficial response in terms of reduced immune activation [45].

Lekva et al. considered oral glucose tolerance test findings, lipid profiles, PTX3 levels, and arterial stiffness in 300 women during pregnancy and 5 years afterwards. Early in pregnancy and 5 years later, PTX3 levels were lower in the women who developed GDM, and they were associated with BMI. Low PTX3 levels in early pregnancy were inversely correlated with metabolic risk factors for CVD (such as body composition, arterial stiffness, dyslipidemia, and a history of GDM) 5 years after delivery. Low plasma concentrations of PTX3 in early pregnancy are therefore associated with the subsequent onset of GDM and a higher risk of CVD later on [46].

6. Conclusions

In conclusion, numerous studies have demonstrated an increased risk of type 2 diabetes, metabolic syndrome, and CVD after pregnancy in women who develop GDM, but the mechanisms contributing to the vascular dysfunction seen in GDM women remain uncertain. For the time being, no

validated markers of this vascular risk are identifiable before the onset of diabetes, metabolic syndrome, or cardiovascular morbidity. Novel potential early markers have recently been proposed, but further investigations on larger samples and longitudinal studies are needed to confirm their value. Given the rising prevalence of GDM, future studies should aim to identify strong early markers of CVD in women who develop this condition, and specific strategies are warranted to prevent or reduce obesity, diabetes, metabolic syndrome, and consequent CVD, in this particular population.

Competing Interests

The authors declare that they have no competing interests.

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Research Article

Cardiometabolic Risk in Hyperlipidemic Men and Women

Michael Leutner,[1] Christian Göbl,[2] Alice Wielandner,[3] Eleonora Howorka,[1] Marlies Prünner,[1] Latife Bozkurt,[4] Jürgen Harreiter,[1] Helmut Prosch,[3] Oliver Schlager,[5] Silvia Charwat-Resl,[5] and Alexandra Kautzky-Willer[1]

[1]*Department of Internal Medicine III, Division of Endocrinology and Metabolism, Unit of Gender Medicine, Medical University of Vienna, Waehringer Guertel 18-20, 1090 Vienna, Austria*
[2]*Department of Gynecology and Obstetrics, Division of Feto-Maternal Medicine, Medical University of Vienna, Waehringer Guertel 18-20, 1090 Vienna, Austria*
[3]*Department of Biomedical Imaging and Image Guided Therapy, Medical University of Vienna, Waehringer Guertel 18-20, 1090 Vienna, Austria*
[4]*Department of Internal Medicine III, Clinical Division of Endocrinology and Metabolism, Medical University of Vienna, Waehringer Giertel 18-20, 1090 Vienna, Austria*
[5]*Department of Internal Medicine II, Division of Angiology, Medical University of Vienna, Waehringer Guertel 18-20, 1090 Vienna, Austria*

Correspondence should be addressed to Alexandra Kautzky-Willer; alexandra.kautzky-willer@meduniwien.ac.at

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Objective. The aim of this study was to evaluate sex specific differences of metabolic and clinical characteristics of treated hyperlipidemic men and women (HL-men and HL-women). *Methods*. In this study vascular and metabolic characteristics of 35 HL-women and 64 HL-men were assessed. In addition a sex specific analysis of metabolic and nutritional habits of HL-patients with prediabetes (HL-IGR) was done. *Results*. HL-women were older and had favourable concentrations of high density lipoprotein cholesterol (HDL-cholesterol), triglycerides (TG), and triglyceride/HDL-cholesterol ratio (TG/HDL-ratio) but were also shown to have higher concentrations of lipoprotein-a compared to HL-men. HL-men were characterized as having higher levels of liver-specific parameters and body weight as well as being more physically active compared to HL-women. Brain natriuretic peptide (pro-BNP) was higher in HL-women than HL-men, while no differences in metabolic syndrome and glycemic parameters were shown. HL-IGR-women were also older and still had a better profile of sex specific lipid parameters, as well as a lower body weight compared to HL-IGR-men. No differences were seen in vascular parameters such as the intima media thickness (IMT). *Conclusion*. HL-women were older and had overall more favourable concentrations of lipid parameters and liver enzymes but did not differ regarding vascular morphology and insulin sensitivity compared to HL-men of comparable body mass index (BMI).

1. Background

In general men have a higher risk of cardiovascular mortality compared to women [1]. In addition to the better outcome in cardiovascular disease (CVD) in women, the time of occurrence of CVD is also later [2]. These discrepancies occur due to the significant influence that sex plays on the development of CVD [1].

One of the major influences on CVD is the lipid profile [3, 4] and it is well known that there are sex specific differences in the progression of CVD affected by hyperlipidemia [5, 6]. In addition studies have shown that menopause and female sex hormones have a big influence on lipid parameters [7]. Studies show that there are also sex specific differences in the reach of target values of lipid parameters. Wenger showed that hyperlipidemic men reach more often the target values of blood parameters compared to women [8].

These discrepancies occur because there are multifactorial sex specific factors which influence the reach of target

[9, 10]. Nevertheless, dyslipidemic treatment reduces the occurrence of CVD in both sexes [11, 12].

In addition to dyslipidemia, prediabetes is also a risk factor for the development of CVD [13]. Studies show that women with high blood glucose levels have a higher risk of cardiovascular mortality compared to men [14–17].

Little is known about the combination of hyperlipidemia with hyperglycemia.

It was shown that there is a cumulative effect of hyperlipidemia and prediabetes on atherosclerosis and the development of coronary heart disease [18, 19].

Therefore, further investigations are necessary. The objective of this analysis is to compare the metabolic and clinic characteristics of hyperlipidemic men and women with and without prediabetes.

2. Methods

The detailed study procedures were previously described [18]. The primary outcome of this study was to compare sex specific differences in treated hyperlipidemic patients. We also studied sex differences in the high risk subgroup with prediabetes in this analysis.

In brief, this study included 35 women and 64 men with hyperlipidemia. The subanalysis of hyperlipidemic patients with prediabetes consisted of 19 women and 29 men. All patients were diagnosed and treated according to the ESC/EAS guidelines [20].

Prediabetes was diagnosed with glycated hemoglobin A1c (HbA1c) levels of ≥5.7% and <6.5% or/and fasting glucose levels of ≥100 mg/dL and <126 mg/dL according to the guidelines of the American Diabetes Association [21].

Inclusion criteria were an age between 35 and 75 years and a consistent dyslipidemic treatment (including diet), for at least the last three months before participating in the study. Patients with diabetes mellitus type-1 or type-2 were excluded from this study [18]. The study participants were divided into two groups according to sex.

Patients had a positive history of CVD if they had been diagnosed with one or more of the following: stroke, coronary heart disease, peripheral artery disease, myocardial infarction, or angina pectoris. Data from a 7-day food intake diary was used for the analysis of the mean daily energy intake (analysed with the program nut.s, nutritional software v1.32.37-2015.12.15, URL: http://www.nutritional-software.at/) in the specific subpopulation of HL-IGR-men and HL-IGR-women. The medical history of the patients was assessed by a questionnaire and anthropometric data such as height, body weight, or waist circumference, as well as the blood pressure, were measured according to standardized procedures [18].

Physical activity was measured using an Omron Walking Style II pedometer. Therefore, study participants were instructed to take the pedometer for 7 days. After the 7 days the mean steps of the pedometer were calculated [18].

2.1. IMT Measurements. IMT measurements were performed by ultrasound and conducted by two experienced coinvestigators according to standardized procedures as previously described [18]. Measurements were obtained by using a 9 MHz linear transducer probe of an Acuson ultrasound machine (Acuson XP 128, Siemens Medical Solutions, USA). IMT was measured by using frozen B-mode images of the far wall of the distal common carotid artery, approximately 1.5–2 cm proximal to the carotid bifurcation. In terms of reaching the values of "good clinical practice" the analysation process was blinded and performed under the supervision of an expert coinvestigator and by an experienced coinvestigator [18].

2.2. Laboratory Measurements. As previously described [18], laboratory parameters were taken in fasting conditions (≥10 hours) and measurements, including serum lipids, fasting plasma glucose, fasting insulin, C-peptide, HbA1c, parameters of liver function, pro-BNP, and high sensitive CRP (hsCRP), were analysed according to international standard laboratory methods at the Department of Medical and Chemical Laboratory Diagnostics (http://www.kimcl.at/).

In accordance with the general guidelines the Friedewald formula was used for the assessment of low density lipoprotein cholesterol (LDL-cholesterol) [22].

2.3. Calculations. We measured insulin sensitivity by using the QUICKI-test [23].

2.4. Statistical Analysis. Means ± standard deviations were stated for normal continuous variables and percentages for categorical variables. Median and interquartile range were stated if variables were not normally distributed (verification with the Shapiro-Wilk-test).

Students t-test and Fisher's exact test were applied for sex specific group comparisons (men versus women). If normality assumption was not given, Wilcoxon rank sum test was used for group based comparisons. Logarithmic transformation was used for parameters which were strongly skewed: ln(TG), ln(TG/HDL-ratio), ln(lipoprotein-a), ln(insulin+1), ln(pro-BNP), ln(hsCRP+1), ln(glutamate-oxaloacetate transaminase, GOT), ln(glutamate-pyruvate transaminase, GPT), and ln(gamma-glutamyl transferase, GGT). Pearson's product moment correlation was used for the analysis of correlations between continuous variables.

In the case of multivariable adjustment linear two-way ANOVA models (modeling interactions between sex and prediabetes on lipid parameters) were used.

Power analysis was performed to determine the sample size needed to achieve 80% test power for the t-test analyses. This analysis was performed using G*Power software, version 3.1.9.2 (software freely available from the University of Düsseldorf). For fasting glucose, a mean difference of 10 mg/dL and a standard deviation of 14 mg/dL were assumed as clinically relevant. Therefore the minimal sample size was calculated as 32 patients per group. For LDL-cholesterol, for a mean difference of 30 mg/dL and assumed standard deviation of 40 mg/dL, the minimal sample size was calculated as 29 patients per group.

The statistical analysis was done with R (V3.1.1) [24]. Statistical significance was assumed with a two-sided p value of ≤0.05.

Table 1: Characteristics of the study sample, divided by sex.

	n (female/male)	Female	Male	p value
Age [years]*	35/64	58.0 ± 10.8	50.4 ± 9.3	0.001
BMI [kg/m^2]*	34/61	27.7 ± 5.5	27.7 ± 3.5	0.998
Body weight	34/61	72.99 ± 13.72	88.47 ± 12.62	<0.001
Waist [cm]*	31/58	91.8 ± 11.6	98.7 ± 12.2	0.011
RRS [mmHg]*	24/45	125.9 ± 14.4	132.2 ± 14.8	0.089
RRD [mmHg]*	24/45	78.5 ± 8.7	81.8 ± 10.4	0.162
TC [mg/dL]*	35/64	243.9 ± 72.3	227.6 ± 74.1	0.290
LDL-C [mg/dL]*	34/60	143.3 ± 59.2	127.1 ± 45.6	0.174
LDL-C < 100 mg/dL	34/60	9 (26.5%)	17 (28.3%)	0.911
HDL-C [mg/dL]*	33/60	65.2 ± 19.6	45.0 ± 15.1	<0.001
NHDL-C [mg/dL]*	33/60	173.1 ± 61.5	172.2 ± 59.3	0.947
ln(TG) [mg/dL]*	35/64	5.1 ± 0.64	5.53 ± 0.82	0.008
ln(TG/HDL)*	33/60	0.89 ± 0.7	1.65 ± 0.87	<0.001
ln(Lip.a) [units]*	30/57	3.5 ± 1.05	2.94 ± 1.22	0.031
IMT-left [mm]*	31/58	0.65 ± 0.18	0.63 ± 0.14	0.584
IMT-right [mm]*	30/56	0.64 ± 0.15	0.63 ± 0.12	0.824
IMT av [mm]*	30/56	0.64 ± 0.14	0.63 ± 0.12	0.711
Glucose [mg/dL]*	34/61	93.4 ± 10.8	94.2 ± 10.7	0.720
ln(insulin+1) [μU/mL]*	32/60	2.05 ± 0.69	2.28 ± 0.67	0.131
C-peptide [ng/mL]*	28/50	2.91 ± 2.07	2.65 ± 1.11	0.546
HbA1c [%]*	35/62	5.61 ± 0.37	5.46 ± 0.38	0.054
QUICKI-test*	29/49	0.37 ± 0.05	0.35 ± 0.04	0.266
ln(proBNP) [units]*	30/55	4.57 ± 0.79	3.77 ± 1.20	<0.001
ln(hsCRP+1) [units]*	30/62	0.30 ± 0.28	0.21 ± 0.21	0.161
ln(GOT) [mg/dL]*	34/64	3.29 ± 0.37	3.38 ± 0.35	0.263
ln(GPT) [mg/dL]*	34/64	3.22 ± 0.47	3.46 ± 0.47	0.021
ln(GGT) [mg/dL]*	34/64	3.28 ± 0.76	3.79 ± 0.82	0.003
Prediabetes**	34/62	19 (55.9)	29 (46.8)	0.522
Ezetimibe**	33/55	3 (9.1)	6 (10.9)	1.000
Nicotinic acid**	33/54	1 (3.0)	4 (7.4)	0.646
Fibrates**	33/54	5 (15.2)	22 (40.7)	0.017
Statins**	33/54	16 (48.5)	38 (70.4)	0.068
CVD**	33/60	2 (6.1)	10 (16.7)	0.202
Mean steps 7 days*	31/47	7230.2 ± 2106.1	8500.1 ± 3395.9	0.045
Metabolic syndrome**	21/44	7 (33.3)	16 (36.4)	1.000
Mean treatment duration of the last taken dyslipidemic medication (days)*	33/62	2068.03 ± 2635.61	1879.77 ± 1997.47	0.721

*t-test, **Chi-square test.

Data are presented as number of observations (n) and means ± standard deviation. BMI (body mass index), waist (waist circumference), RRS (systolic blood pressure), RRD (diastolic blood pressure), TC (total cholesterol), LDL-C (low density lipoprotein cholesterol), HDL-C (high density lipoprotein cholesterol), NHDL-C (non-high density lipoprotein cholesterol), TG (triglycerides), TG/HDL (triglyceride/HDL-cholesterol ratio), Lip.a (lipoprotein (a)), IMT (carotid intima media thickness), HbA1c (glycated hemoglobin A1c), QUICKI (quantitative insulin sensitivity check index), proBNP (pro B-type natriuretic peptide), hsCRP (high sensitive C-reactive protein), GOT (glutamate-oxaloacetate transaminase), GPT (glutamate-pyruvate transaminase), GGT (gamma-glutamyl transferase), and CVD (cardiovascular disease).

3. Results

In this study 35 HL-women and 64 HL-men were included. A descriptive comparison of study participants, divided by sex, is shown in Table 1. This table shows that HL-women were older and had a lower body weight and waist circumference but did not differ regarding BMI and the systolic and diastolic blood pressure compared to HL-men. HL-women were shown to have better concentrations of lipid parameters such as HDL-cholesterol, TG, and TG/HDL-ratio but had higher concentrations of lipoprotein-a compared to HL-men (Table 1). No sex specific difference was shown in the occurrence of LDL-cholesterol levels < 100 mg/dL. Univariable comparisons showed that there was no significant difference in carotid IMT measurements between HL-men and HL-women. In addition, no sex specific differences in the glucose metabolism (glucose, insulin, C-peptide, HbA1c, and QUICKI-test) were found. HL-women were also shown to have higher levels of traditional cardiovascular risk marker pro-BNP, but not hs-CRP (Table 1).

Table 2: Characteristics of the study sample with prediabetes, divided by sex.

	n (female/male)	Female	Male	p value
Age [years]*	19/29	62.4 ± 9.6	54.4 ± 9.8	0.007
Body weight	19/28	73.50 ± 13.62	90.49 ± 13.55	<0.001
BMI [kg/m^2]*	19/28	27.8 ± 4.8	28.9 ± 3.7	0.360
Waist [cm]*	18/27	94.9 ± 9.2	104.4 ± 8.9	0.001
RRS [mmHg]*	14/20	127.5 ± 17.6	136.4 ± 18.2	0.164
RRD [mmHg]*	14/20	77.2 ± 10.7	82.1 ± 11.5	0.223
TC [mg/dL]*	19/29	238.6 ± 68.3	231.6 ± 81.5	0.371
LDL-C [mg/dL]*	18/27	136.2 ± 50.2	131.5 ± 45.4	0.746
HDL-C [mg/dL]*	17/27	62.7 ± 16.1	43.7 ± 14.6	<0.001
NHDL-C [mg/dL]*	17/27	164.3 ± 47.4	171.5 ± 50.5	0.640
ln(TG) [mg/dL]*	19/29	5.2 ± 0.69	5.55 ± 0.76	0.165
ln(TG/HDL)*	17/27	0.97 ± 0.66	1.70 ± 0.81	0.003
ln(Lip.a) [units]*	17/26	4.00 ± 1.04	2.96 ± 1.40	0.013
IMT-left [mm]*	17/26	0.68 ± 0.18	0.69 ± 0.17	0.576
IMT-right [mm]*	17/26	0.69 ± 0.16	0.66 ± 0.14	0.463
IMT av [mm]*	17/26	0.69 ± 0.15	0.68 ± 0.14	0.834
Glucose [mg/dL]*	19/27	99.8 ± 9.2	100.3 ± 12.0	0.882
ln(insulin+1) [μU/mL]*	17/27	2.15 ± 0.77	2.41 ± 0.75	0.273
C-peptide [ng/mL]*	16/23	3.44 ± 2.55	3.03 ± 1.16	0.656
HbA1c [%]*	19/28	5.83 ± 0.32	5.73 ± 0.33	0.322
QUICKI-test*	16/23	0.36 ± 0.05	0.35 ± 0.05	0.478
ln(proBNP) [units]*	16/23	4.18 ± 0.61	4.23 ± 1.51	0.905
ln(hsCRP+1) [units]*	17/28	0.30 ± 0.29	0.20 ± 0.17	0.440
ln(GOT) [mg/dL]*	18/29	3.34 ± 0.35	3.41 ± 0.37	0.499
ln(GPT) [mg/dL]*	18/29	3.32 ± 0.45	3.55 ± 0.46	0.098
ln(GGT) [mg/dL]*	18/29	3.52 ± 0.78	3.96 ± 0.70	0.048
Ezetimibe**	19/23	2 (10.5)	3 (13.0)	1.000
Nicotinic acid**	19/23	0 (0.0)	2 (8.7)	0.556
Fibrates**	19/23	2 (10.5)	9 (39.1)	0.081
Statins**	19/23	11 (57.9)	19 (82.6)	0.155
CVD**	18/27	1 (5.6)	8 (29.6)	0.110
Mean steps 7 days*	17/21	7009.8 ± 2520.4	8381.4 ± 2660.0	0.114
Metabolic syndrome**	12/20	5 (41.7)	12 (60.0)	0.522
Mean treatment duration of the last taken dyslipidemic medication (days)*	18/28	2272.3 ± 2649.9	2132.8 ± 2362.1	0.938

*t-test, **Chi-square test.

Data are presented as number of observations (n) and means ± standard deviation. BMI (body mass index), waist (waist circumference), RRS (systolic blood pressure), RRD (diastolic blood pressure), TC (total cholesterol), LDL-C (low density lipoprotein cholesterol), HDL-C (high density lipoprotein cholesterol), NHDL-C (non-high density lipoprotein cholesterol), TG (triglycerides), TG/HDL (triglyceride/HDL-cholesterol ratio), Lip.a (lipoprotein (a)), IMT (carotid intima media thickness), HbA1c (glycated hemoglobin A1c), QUICKI (quantitative insulin sensitivity check index), proBNP (pro B-type natriuretic peptide), hsCRP (high sensitive C-reactive protein), GOT (glutamate-oxaloacetate transaminase), GPT (glutamate-pyruvate transaminase), GGT (gamma-glutamyl transferase), and CVD (cardiovascular disease).

HL-men in this study were characterized as being more physically active (mean steps in 7 days) and as having significantly higher liver-specific parameters (GGT, GPT). No sex specific differences were observed in the occurrence of a history of CVD and of the metabolic syndrome (Table 1).

4. Sex Specific Subanalysis of HL-Patients with Prediabetes Including Nutritional Data

In addition to the analysis above, a subanalysis of 19 women and 29 men with hyperlipidemia additionally affected by a prediabetes was done. A descriptive comparison of study participants, divided by sex, is shown in Table 2.

This table shows that HL-IGR-women were older and had a lower body weight and waist circumference but did not differ in other anthropometric parameters such as BMI and the systolic and diastolic blood pressure compared to HL-IGR-men. There was no significant difference in modifiable lipid parameters (total cholesterol, LDL-cholesterol, and TG) between sexes. HL-IGR-women were shown to have significantly higher levels of HDL-cholesterol and lipoprotein-a, as well as favourable concentrations of

Table 3: Nutritional characteristics of the study sample with prediabetes, divided by sex.

	n (female/male)	Female	Male	p value
Total energy intake (kcal)*	14/20	1386.6 ± 388.9	1790.0 ± 693.6	0.104
Fat (mg)*	14/20	53456.7 ± 20456.9	61750.4 ± 30408.8	0.381
Cholesterol (mg)*	14/20	207 ± 99.4	297.4 ± 153.9	0.063
Omega-3 fatty acids (mg)*	14/20	1700.8 ± 978.5	1767.6 ± 1032.6	0.796
Omega-6 fatty acids (mg)*	14/20	7807.6 ± 3722.0	8100.2 ± 3762.5	0.824
Polyunsaturated fatty acids (mg)*	14/20	9511.2 ± 4487.1	10284.0 ± 4786.2	0.638
Saturated fatty acids (mg)*	14/20	22987.7 ± 10056.8	27342.2 ± 13537.4	0.315
Monounsaturated fatty acids (mg)*	14/20	17529.6 ± 6988.6	29249.2 ± 30968.1	0.097
Carbohydrates (mg)*	14/20	157769.7 ± 40805.0	177359.1 ± 79750.7	0.356
Disaccharides (mg)*	14/20	38443.8 ± 18889.7	35274.7 ± 25976.0	0.457
Lactose (mg)*	14/20	7232.8 ± 8305.5	6326.8 ± 7283.3	0.738
Sucrose (mg)*	14/20	30101.6 ± 12942.5	28658.6 ± 23784.8	0.416
Monosaccharides (mg)*	14/20	26831.4 ± 10530.5	27196.4 ± 17224.5	0.944
Fructose (mg)*	14/20	15225.3 ± 6670.6	14812.5 ± 9728.1	0.892
Glucose (mg)*	14/20	11032.1 ± 3862.8	11869.7 ± 7680.7	0.679
Glycogen (mg)*	14/20	33.6 ± 56.1	239.0 ± 255.9	0.001
Vitamin B12 (μg)*	14/19	3.0 ± 1.6	4.6 ± 1.9	0.011
Dietary fiber (mg)*	14/20	18009.2 ± 5366.7	20243.3 ± 10600.1	0.904
Protein (mg)*	14/19	55761.9 ± 20497.3	77520.9 ± 27476.4	0.018

*t-test.
Data are presented as number of observations (n) and means ± standard deviation.

TG/HDL-ratio compared to HL-IGR-men. No difference was found in carotid IMT measurements between HL-IGR-men and HL-IGR-women. In addition, no differences in glucose metabolism (glucose, insulin, C-peptide, HbA1c, and QUICKI-test) and in cardiovascular risk markers (pro-BNP, hsCRP) between sexes were found in this specific subanalysis (Table 2).

HL-IGR-men were shown to have higher liver-specific parameters (GGT, Table 2). Table 3 shows that glycogen, vitamin-B12, and protein intake, measured with a dietary protocol, were significantly higher in HL-IGR-men.

As shown in Table 4 sex specific analyses revealed that waist circumference is related to concentrations of TG in HL-IGR-women, but not in HL-IGR-men. No association with waist circumference was observed for any other lipid parameters (LDL-cholesterol, HDL-cholesterol, total cholesterol, and TG in men) or parameters of glucose metabolism (fasting plasma glucose, HbA1c) in both sexes. In addition no correlation of waist circumference with IMT in both sexes was found. Table 4 also shows that there was no association for body weight and BMI with lipid parameters and parameters of glucose metabolism in HL-IGR-men and HL-IGR-women. In general no interactions between sex and prediabetes with lipid parameters (LDL-cholesterol, HDL-cholesterol, TG, and total cholesterol) were found.

5. Discussion

HL-women are characterized as being older and having a lower body weight and waist circumference, more favourable concentrations of HDL-cholesterol, TG, and TG/HDL-ratio, and better concentrations of liver enzymes, but they do not differ regarding insulin sensitivity and the IMT compared to HL-men. The metabolic characteristics of HL-IGR-men and HL-IGR-women are in general comparable with the metabolic characteristics of the whole study population.

The fact that HL-women have favourable concentrations of certain lipid parameters (HDL-cholesterol, TG/HDL-ratio) is a well described sex specific difference in various conditions. In general men have a higher risk of CVD compared to women [1]. The higher levels of HDL-cholesterol in women are one of the major protective factors against developing CVD, which leads to a later occurrence of cardiovascular disease in women [2]. Female sex hormones relate to higher HDL-cholesterol levels in women and exert overall protective effects against CVD [25, 26]. In our study population there were no significant sex specific differences in modifiable lipid parameters, such as LDL-cholesterol or total cholesterol. Only the concentrations of TG were shown to be significantly lower in female participants. This is an interesting point because studies showed that women were less likely to reach treatment goals of lipid parameters compared to men [27–29]. So the similarity of lipid parameters, such as LDL-cholesterol or total cholesterol between the sexes in our study, could point out that the previously described sex specific differences in reach of target values of lipid parameters faded. To support this hypothesis our results showed that there is no sex specific difference in the presence of LDL-cholesterol levels < 100 mg/dL in this study. The fact that HL-women have higher concentrations of cardiovascular risk marker pro-BNP could point to a higher risk for CVD. Wang et al. showed that women have in general higher concentrations of natriuretic peptide (NP) [30], which positively correlate with estrogen concentrations [31, 32]. Lam et al. also showed

Table 4: Correlation analysis of parameters of body composition with cardiovascular and metabolic characteristics divided by sex in HL-IGR-patients.

	Body weight		BMI		Waist circumference	
	rho	*p* value	rho	*p* value	rho	*p* value
HL-IGR-men						
LDL-cholesterol	−0.10	NS	−0.13	NS	−0.10	NS
HDL-cholesterol	−0.14	NS	−0.19	NS	−0.04	NS
Total cholesterol	−0.00	NS	−0.05	NS	−0.03	NS
Triglycerides	0.16	NS	0.23	NS	0.06	NS
HbA1c	−0.00	NS	−0.13	NS	0.17	NS
Fasting plasma glucose	0.08	NS	0.01	NS	0.18	NS
HL-IGR-women						
LDL-cholesterol	−0.11	NS	−0.14	NS	−0.01	NS
HDL-cholesterol	−0.24	NS	−0.21	NS	−0.07	NS
Total cholesterol	−0.09	NS	−0.07	NS	0.06	NS
Triglycerides	0.35	NS	0.36	NS	**0.49**	**0.04**
HbA1c	−0.02	NS	0.25	NS	0.11	NS
Fasting plasma glucose	0.10	NS	0.16	NS	0.33	NS

that women in menopause have still higher concentrations of NP compared to men. Additionally they showed that testosterone has a decreasing effect on the concentrations of NP in men [33]. Nevertheless Kannel showed that women in the postmenopausal status have a significant increase in the development of CVD [34]. So larger and longitudinal studies are required in order to find conclusive results, whether the higher concentration of pro-BNP is due to sex hormones in this specific population.

In general the metabolic characterization of the high risk population of HL-IGR-women and men is comparable with the results of the whole study population above.

Although there were not any significant sex specific differences in traditional cardiovascular risk markers in the specific population of HL-IGR-patients, it can be speculated that the cohort of HL-IGR-women is at higher risk for mortality compared to HL-IGR-men because in addition to hyperlipidemia, hyperglycemia is, especially in women, a higher risk factor for cardiovascular mortality compared to men [15–17].

Therefore, it has to be reported that atherogenic dyslipidemia, including reduced levels of HDL-cholesterol and increased levels of small dense LDL particles and triglycerides, is a feature of prediabetes. This interrelationship between impaired glucose regulation and lipid abnormalities leads in further consequence to an increased risk of developing CVD, indicating that HL-IGR-patients could be a high risk population [35].

Despite the lack of significance regarding the occurrence of CVD, men showed a higher occurrence rate (29.6%) compared to women (5.6%) in this study. This number seems to be plausible because men have in general a higher risk of developing CVD [1] with an earlier onset [2]. Nevertheless the specific subpopulation of treated HL-IGR-women around menopause could be a high risk population which should be monitored and treated to target more thoroughly. Interestingly in our study it was shown that there is a positive correlation of triglycerides with waist circumference in HL-IGR-women, but not in men. So an adverse body composition could be a higher risk factor for metabolic diseases in HL-IGR-women. Therefore, larger studies are required to investigate these sex specific differences.

One major limitation of this study is the low number of participants and that prediabetes was diagnosed using fasting blood parameters and not the oral glucose tolerance test. In addition the difference in the mean ages is a further limitation.

We are aware that with our study design smaller effects could have been missed. This study has an exploratory character and should show the sex specific cardiometabolic characteristics in the specific population of treated hyperlipidemic men and women. Nevertheless a greater number of study participants would be needed in order to investigate the real risk of this specific population.

In conclusion HL-women were older and had overall more favourable concentrations of lipid parameters and liver enzymes but did not differ regarding vascular morphology and insulin sensitivity compared to men of comparable BMI. Nevertheless the age of menopause could be a major risk factor for CVD. So HL-women, especially after menopause, should be treated and observed more carefully, not only regarding hyperlipidemia, but also regarding hyperglycemia. Larger studies should be done in order to evaluate the real risk of this specific subpopulation.

Competing Interests

The authors have no competing interests.

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Research Article

Stroke Risk among Patients with Type 2 Diabetes Mellitus in Zhejiang: A Population-Based Prospective Study in China

Lihua Guo, Min Yu, Jieming Zhong, Haibin Wu, Jin Pan, Weiwei Gong, Meng Wang, Fangrong Fei, and Ruying Hu

Zhejiang Provincial Center for Disease Control and Prevention, 3399 Binsheng Road, Hangzhou 310051, China

Correspondence should be addressed to Ruying Hu; ryhu1234@163.com

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Objective. This study aimed to explore the incidence of stroke and stroke subtypes among patients with type 2 diabetes mellitus (T2DM) based on the long-term surveillance data in Zhejiang, China, during 2007 to 2013. *Materials and Methods*. During January 1, 2007, and December 31, 2013, a total of 327,268 T2DM and 307,984 stroke patients were registered on Diabetes and Stroke Surveillance System, respectively. Stroke subtypes were classified according to standard definitions of subarachnoid hemorrhage, intracerebral hemorrhage, and ischemic stroke. The incidence of stroke and stroke subtypes was calculated by standardized incidence ratio (SIRs) with 95% confidence intervals (CIs) compared with general population. *Results*. The incidence of stroke and stroke subtypes among patients with T2DM was significantly higher than in general population. Stroke risk was found significantly increased with an SIR of 3.87 (95% CI 3.76–3.99) and 3.38 (95% CI 3.27–3.48) in females and males, respectively. The excess risk of stroke was mainly attributable to the significantly higher risk of cerebral infarctions with the risk for T2DM being four times that for general population. *Conclusions*. The relationship between stroke and T2DM was strong, especially in female. The incidence of stroke and stroke subtypes among patients with T2DM was up to 3-fold higher than in general population in Zhejiang province, especially the subtype of cerebral infarctions.

1. Introduction

Stroke has been recognized as a major problem for public health worldwide. As World Health Organization reported, stroke ranks third (after MI and cancer) as a cause of death around the world [1]. Although stroke incidence has declined in industrialized countries [2], it has increased among urban [3] and rural [4] residents in China over past decades. The prevalence of type 2 diabetes mellitus (T2DM) in Chinese adults has increased faster, too [5]. In Western population, many prospective studies have shown that, compared to population without diabetes, the incidence and mortality of stroke were increased in patients with diabetes [6–9]. The Da Qing IGT and Diabetes Study found that diabetes was associated with a substantially increased risk of death in Chinese adults, especially from CVD, almost half of which was due to stroke [10]. The result of a Chinese hospital-based study showed patients with diabetes presented more frequently with stroke compared with nondiabetics [11]. However, these studies have been performed in selected patients based on hospital. Furthermore, due to studies with small sample sizes, there was insufficient data to describe the stroke incidence in patients with T2DM. To our knowledge, the stroke incidence in patients with T2DM compared to general population is still unknown in Chinese adults, especially population-based. Dependent on Diabetes Surveillance System and Stroke Surveillance System in Zhejiang province, this study aims to use population-based surveillance data to describe the incidence of stroke and stroke subtypes among patients with T2DM.

2. Materials and Methods

2.1. Data Sources. The long-term surveillance data was from Diabetes Surveillance System and Stroke Surveillance System of Zhejiang Province in China, which was established in 2001 with thirty surveillance districts and covered about 16 million residents. These surveillance districts were selected

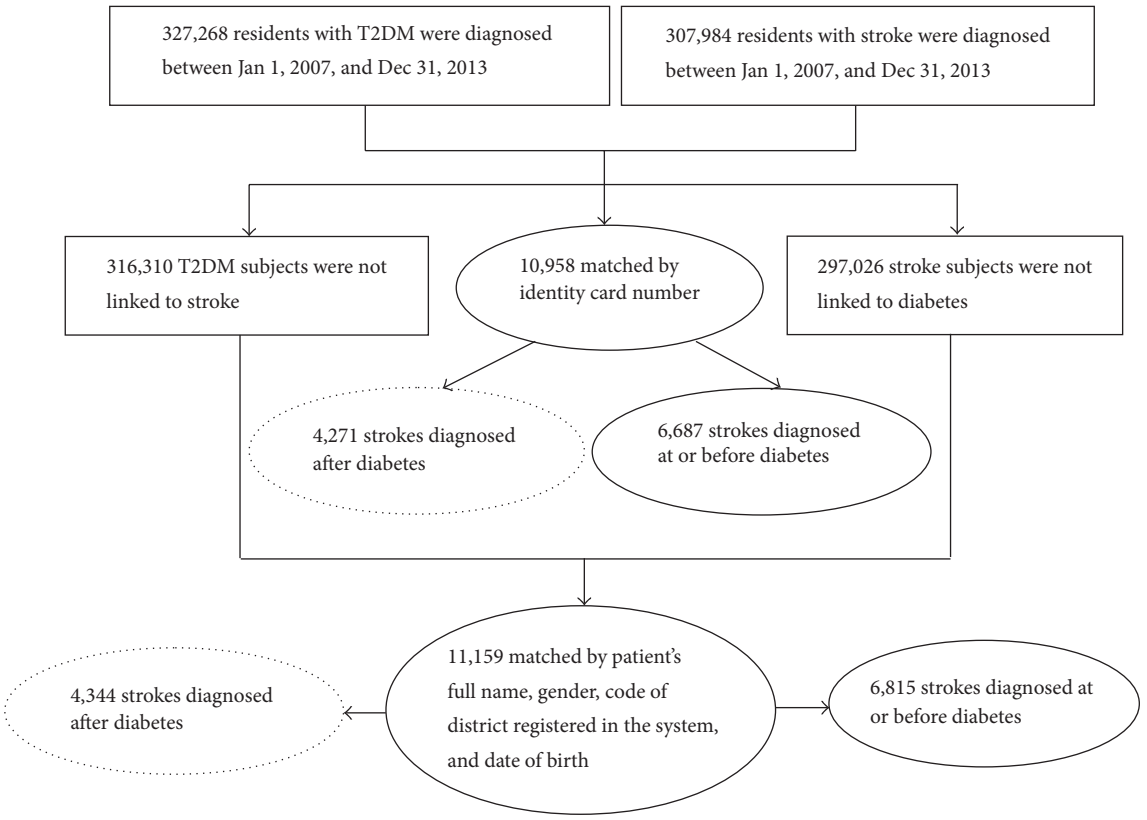

Figure 1: Flowchart of data linkage between Diabetes Surveillance System and Stroke Surveillance System of Zhejiang in China.

by geographic variations and socioeconomic status which showed appropriate representativeness for Zhejiang Province [12]. The diabetes and stroke patients were diagnosed by certificated health practitioner and must be reported within a week. Patients' information including demographics, diagnosis, and diagnostic basis was registered in the surveillance system. Then the records were transferred to regional Center for Disease Control and Prevention (CDC) for examination and verification, and the eligible records were pooled together to provincial CDC for further verification to make sure the record was the newly diagnosed and did not report before [13].

For stroke, if the interval between first onset and recurrence was more than 28 days, this record needs to report again. Otherwise, this record need not to report. According to the International Classification of Disease 10th revision (ICD-10), stroke patients were divided into four stroke subtypes, including subarachnoid hemorrhage (I60), intracerebral hemorrhages (I61), cerebral infarctions (I63), and unspecified strokes (I64). Classification and registration were completed by professional health practitioner. Furthermore, in the Diabetes Surveillance System, diabetes was divided into type 1, type 2, gestational, or other types of diabetes. Finally, a total of 327,268 T2DM patients and 307,984 stroke patients were collected between January 1, 2007, and December 31, 2013. This study was carried out in accordance with the "Declaration of Helsinki."

2.2. Data Linkage. In the present study, only the stroke and T2DM patients recorded between January 1, 2007, and December 31, 2013, were included. Two kinds of matching conditions were used to link databases. (1) Identity card number was used to link T2DM patients who suffer stroke in the following years. (2) Patient's full name, gender, code of district registered in the system, and date of birth (year and month) were simultaneously used to link the record which did not match in step one (Figure 1). Those paired records with the date of initial T2DM diagnosis later than stroke were excluded. Finally, 8615 cases of T2DM patients suffering stroke were paired.

2.3. Statistical Analysis. The incidence of stroke and stroke subtypes among patients with T2DM was evaluated by standardized incidence ratio (SIR) and 95% confidence interval (CI) comparing with general population. SIR and 95% CI were calculated as the number of observed stroke events divided by the excepted number of events with the Poisson regression model [14]. The numbers of observed stroke events were counted by T2DM patients who suffer stroke in the follow-up years. The excepted number of events was calculated as the number of person-year at risk multiplied by the stroke incidence in general population. The number of person-year at risk was calculated for T2DM patients in both paired and unpaired groups, respectively. For the paired group, person-years were calculated from the data

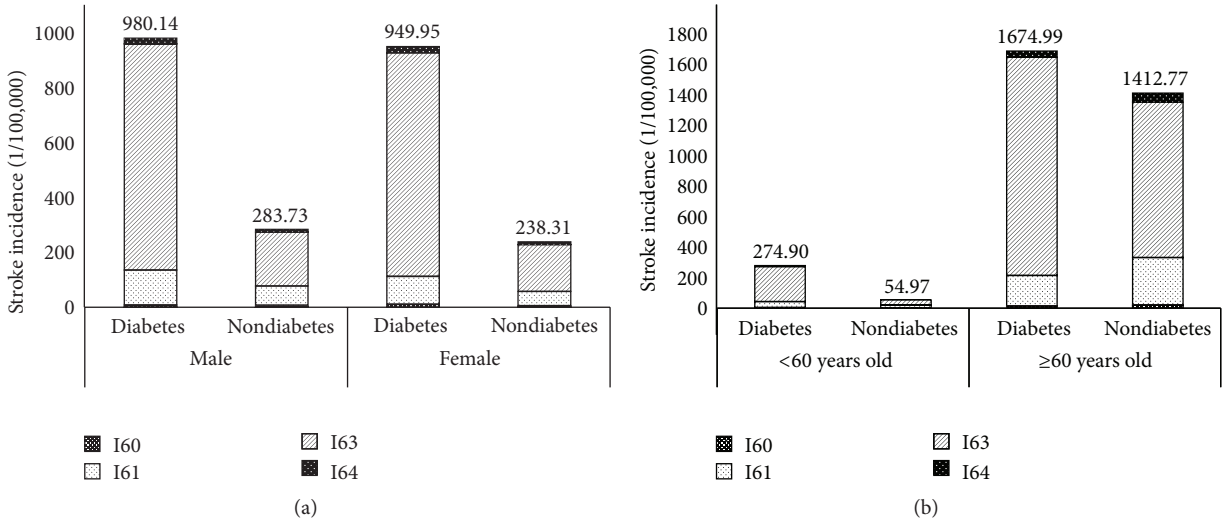

Figure 2: Stroke incidence for the diabetic and nondiabetic populations by age and sex in 2007–2013 in Zhejiang Province. (a) Stroke incidence in male and female. (b) Stroke incidence grouped by age. I60: subarachnoid hemorrhage; I61: intracerebral hemorrhages; I63: cerebral infarctions; and I64: unspecified strokes.

Table 1: Characteristics of the T2DM and stroke cases included in study.

	T2DM	Stroke
Total	327,268	8,615
Gender, *N* (%)		
Male	163,819 (50.06)	4,324 (50.19)
Female	163,449 (49.94)	4,291 (48.81)
Area, *N* (%)		
Urban	130,807 (39.97)	3,166 (36.75)
Rural	196,461 (60.03)	5,449 (63.25)
Age at diagnosis, median (*Q*1, *Q*3)	59 (50,69)	72 (64,79)
Age at registration, median (*Q*1, *Q*3)	60 (51,69)	72 (64,79)

of initial diagnosis of T2DM to the occurrence of stroke. For the unpaired group, person-years were calculated from the data of initial diagnosis of T2DM to the dateline of this study (December 31, 2013). The stroke incidence in general population used stroke incidence of residents in thirty surveillance districts. All analyses were done by using SAS 9.2 (SAS Institute Inc., Cary, NC, USA).

3. Results

A total of 327,268 T2DM cases were included from Diabetes Surveillance System between January 1, 2007, and December 31, 2013. During the follow-up time, 8615 stroke events have occurred with 4324 (50.19%) in male and 4291 (48.81%) in female, respectively. The median ages at diagnosis and registration of diabetes were 59 (50, 69) years old and 60 (51, 69) years old, respectively. The baseline characteristics of T2DM and total stroke outcomes were described in Table 1.

Table 2 showed gender-specific stroke incidence among patients with T2DM and general population. For all patients, the incidence of total stroke among patients with T2DM was 3.60 times compared to general population. For male patients, the SIR for total stroke was 3.38 (95% CI 3.27–3.48). Four subtypes all showed significant increased SIRs for patients with T2DM compared to general population. Cerebral infarctions (I63) had highest SIR compared to other subtypes as 4.08 (95% CI 3.95–4.22). For female patients, the SIR for total stroke was slightly higher than male as 3.87 (95% CI 3.76–3.99). The SIRs increased significantly among four subtypes, especially in cerebral infarctions (I63) (4.60, 95% CI 4.45–4.75). The incidence of total stroke for the T2DM and general population was higher in male compared with female. However, the SIRs in female were higher than male in total stroke. In addition, the stroke incidence per 100,000 person-years for the diabetic and nondiabetic population in male was higher than female as 980.14 and 283.73, respectively (Figure 2).

Table 3 showed the stroke incidence in patients with T2DM and general population between urban and rural area. For urban and rural area, the SIRs for total stroke were 3.36 (95% CI 3.25–3.48) and 3.77 (95% CI 3.67–3.87), respectively. Four subtypes all showed significant increased SIRs for patients with T2DM. The highest SIRs were in the group of cerebral infarctions (I63) which was 3.98 in urban and 4.57 in rural. The stroke incidence and SIRs in rural area were all higher than in urban area.

According to the age at diagnosis of T2DM, the result of overall SIRs for stroke in patients with T2DM was shown in Table 4. Significant difference was detected for total stroke by age. The incidence of strokes among the population over 60 years old was much higher than the population less than 60 years old. However, the condition of SIR was opposite. In the group of <60 years old, T2DM patients suffer increased risk of stroke compared to the general population except subarachnoid hemorrhage (I60). In the group of ≥60 years old, the SIR increased significantly only in cerebral

Table 2: SIRs in male and female with T2DM compared with general population, 2007–2013 (1/100,000 person-years).

Subtypes	Total					Male					Female				
	Diabetes		General population		SIR (95% CI)	Diabetes		General population		SIR (95% CI)	Diabetes		General population		SIR (95% CI)
	N	Incidence	*N*	Incidence		*N*	Incidence	*N*	Incidence		*N*	Incidence	*N*	Incidence	
Total	8615	964.84	307806	268.10	3.60 (3.52–3.68)	4324	980.14	169029	290.36	3.38 (3.27–3.48)	4291	949.95	138774	245.20	3.87 (3.76–3.99)
I60	83	9.30	6306	5.49	1.69 (1.36–2.10)	37	8.39	2974	5.11	1.64 (1.19–2.27)	46	10.18	3332	5.89	1.73 (1.30–2.31)
I61	1031	115.47	72332	63.00	1.83 (1.72–1.95)	563	127.62	42674	73.31	1.74 (1.60–1.89)	468	103.61	29658	52.40	1.98 (1.81–2.16)
I63	7309	818.57	217537	189.48	4.32 (4.22–4.42)	3634	823.73	117424	201.72	4.08 (3.95–4.22)	3675	813.58	100110	176.89	4.60 (4.45–4.75)
I64	192	21.50	11631	10.13	2.12 (1.84–2.45)	90	20.40	5957	10.23	1.99 (1.62–2.45)	102	22.58	5674	10.03	2.25 (1.86–2.73)

I60: subarachnoid hemorrhage; I61: intracerebral hemorrhages; I63: cerebral infarctions; I64: unspecified strokes.

Table 3: SIRs in urban and rural with T2DM compared with general population, 2007–2013 (1/100,000 person-years).

Subtypes	Urban					Rural				
	Diabetes		General population		SIR (95% CI)	Diabetes		General population		SIR (95% CI)
	N	Incidence	*N*	Incidence		*N*	Incidence	*N*	Incidence	
Total	3166	870.00	102779	258.62	3.36 (3.25–3.48)	5449	1030.08	205027	273.13	3.77 (3.67–3.87)
I60	31	8.52	2268	5.71	1.49 (1.05–2.12)	52	9.83	4038	5.38	1.83 (1.39–2.40)
I61	403	110.74	23798	59.88	1.85 (1.68–2.04)	628	118.72	48534	64.65	1.84 (1.70–1.99)
I63	2667	732.88	73269	184.36	3.98 (3.83–4.13)	4642	877.53	144268	192.19	4.57 (4.43–4.70)
I64	65	17.86	3444	8.67	2.06 (1.62–2.63)	127	24.01	8187	10.91	2.20 (1.85–2.62)

I60: subarachnoid hemorrhage; I61: intracerebral hemorrhages; I63: cerebral infarctions; I64: unspecified strokes.

Table 4: SIRs in age at diagnosis of T2DM compared with general population, 2007–2013 (1/100,000 person-years).

Subtypes	<60 years old					≥60 years old				
	Diabetes		General population		SIR (95% CI)	Diabetes		General population		SIR (95% CI)
	N	Incidence	*N*	Incidence		*N*	Incidence	*N*	Incidence	
Total	1245	274.90	54611	56.16	4.89 (4.63–5.17)	7370	1674.99	253150	1441.32	1.16 (1.14–1.19)
I60	19	4.21	2791	2.87	1.47 (0.94–2.30)	64	15.01	3514	20.01	0.75 (0.58–0.96)
I61	177	39.24	17051	17.53	2.24 (1.93–2.59)	854	199.64	55261	314.63	0.63 (0.59–0.68)
I63	1030	227.64	33710	34.67	6.57 (6.18–6.98)	6279	1433.67	183804	1046.50	1.37 (1.34–1.40)
I64	19	4.22	1059	1.09	3.87 (2.47–6.07)	173	40.56	10571	60.19	0.67 (0.58–0.78)

I60: subarachnoid hemorrhage; I61: intracerebral hemorrhages; I63: cerebral infarctions; I64: unspecified strokes.

infarctions (I63) with 1.37 times higher than in general population.

4. Discussion

This study aimed to explore the subsequent stroke incidence in patients with T2DM based on the long-term surveillance data in Zhejiang province, China. The results showed that the stroke incidence in patients with T2DM was significantly higher than in general population, which were consistent with previous studies [7, 15–17].

The risk for stroke among patients with T2DM was up to 3-fold higher than in general population in male and female, which were comparable to those in large prospective studies [6, 18]. The results of United Kingdom Prospective Diabetes Study (UKPDS) showed that the risk of stroke incidence in patients with T2DM in male was 1.63 times more than in female [19]. The Renfrew/Paisley Study in Scotland [16] and a meta-analysis of 64 cohorts [20] showed that the excess risk of stroke associated with diabetes is significantly higher in female than in male. In the current study, the SIR in female with T2DM was higher than in male in total stroke and all four subtypes. This revealed that, compared to general female population, female with T2DM might have higher risk for stroke. However, the incidence of stroke among general population was higher in male than in female, which was consistent with the result of Sino-MONICA-Beijing Project [3].

The incidence of stroke in rural areas among general population in this study was lower than Tianjin Brain study during 2006–2012 [4] while in urban areas it was higher than Bin Jiang's study during 1991–2000 [21]. It is lacking related study focus on the incidence of stroke in patients with T2DM in China stratified by urbanization level. The risk of stroke in patients with T2DM living in rural areas was 3.77 times than in general population and 3.36 times in urban areas. SIR in rural was higher than in urban areas which was the same as the relationship of stroke incidence among general population between rural and urban area. The reason might be that metabolic control was worse in the rural area in Zhejiang province [22].

Bell found that the relative risk of stroke in patients with T2DM reached a maximum in the 40- to 60-year-old group than in the nondiabetic population [23]. In addition, Kissela et al. found that diabetes is clearly one of the most important risk factors for ischemic stroke, especially in those patients who are less than 65 years of age [24]. This study found that SIR of T2DM patients' age at diagnosis of T2DM less than 60 years old was significantly higher than that of general population. This result was comparable to previous study. However, it was on the contrary to the stroke incidence in general population. It suggested that it was necessary to strengthen the management of patients with T2DM from middle age.

There was a thrombotic tendency or at least an imbalance between the haemostatic and thrombosis-protecting system in diabetic patients, which might play a crucial role in the development of stroke, especially cerebral infarctions (I63) [25]. In this study, the risk of I63 in patients with T2DM was up to 4-fold higher than in general population, higher than the found in the Honolulu Heart Program [26]. Previous studies [11, 27, 28] in diabetic patients have shown a decrease prevalence of both I60 and I61 when compared with the general population. In the current study, the risks of I60, I61, and I64 in patient with T2DM were higher than in general population, which were not consistent with previous studies. This might be due to the fact that other risk factors did not adjust in the study, such as hypertension, cholesterol, and smoking. In one word, the results revealed that T2DM patients had higher risk to suffer I63 than the other three stroke subtypes.

There were several strengths for this study. Firstly, it was one of the few studies exploring the stroke incidence in patients with T2DM by SIR in China. Secondly, it was a population-based surveillance study with a large sample of 327,268 T2DM cases and 8615 stroke event outcomes. The most important is that T2DM and stroke patients were diagnosed and reported by certificated health practitioners, and, to further ensure the quality and veracity of data, the related data was verified by regional and provincial CDCs and registered in the surveillance system eventually.

However, there were some limitations in this study. Firstly, we stratified by the variables of gender, urbanization, and age, while other potential confounding factors including hypertension, cholesterol, smoking, obesity status, alcohol consumption, physical activity, and diabetes treatments have not been adjusted in the analysis. Secondly, the follow-up time was not long enough, which restricted our ability to further assess the potential lead time bias and explore the effect of diabetes duration on stroke incidence.

In conclusion, the current study indicated that the incidence of stroke and stroke subtypes among patients with T2DM was up to 3-fold higher than in general population in Zhejiang province, especially the subtype of cerebral infarctions (I63). Compared to males, the SIR was higher in females, although the incidence of stroke for the diabetic in females was lower than in males. Given the rapid growth of diabetes in China, even a small increased stroke risk would have important public health implications at population level. It is urgent and necessary to prevent and control diabetes.

Competing Interests

The authors declare no conflict of interests.

Acknowledgments

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