Sex disparity in the management and outcomes of dyslipidemia of diabetic patients in the Arabian Gulf: findings from the CEPHEUS study

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Abstract

Background: Little is known about sex gap in the management and outcomes of dyslipidemia among diabetics in the Arabian Gulf. The aim if this study was to determine sex differences in the management and outcomes of dyslipidemia in diabetic patients in the Arabian Gulf.

Methods: This study was derived from the Centralized Pan-Middle-East Survey on the management of hypercholesterolemia. Patients recruited were aged ≥18 years on lipid lowering drugs for ≥3 months (stable medication for ≥6 weeks). Outcomes were based on the joint Consensus Statement of the American Diabetes Association and American College of Cardiology Foundation. Analyses were performed using univariate and multivariate logistic regression techniques.

Results: The mean age of the cohort (n = 3336) was 57 ± 11 years and 45% (n = 1486) were females. Females were less likely to be on rosuvastatin (7.6% vs 12%; P < 0.001), atorvastatin (41% vs 46%; P = 0.005) and combination hypolipidemic therapy (5.6% vs 2.8%; P < 0.001) but more likely to be on simvastatin (51% vs 39%; P < 0.001) than males. Females, especially those with very high atherosclerotic cardiovascular disease (ASCVD) risk status, were also less likely to achieve LDL-cholesterol [adjusted odds ratio (aOR), 0.58; 95% confidence interval (CI): 0.40–0.86; P = 0.006], non-HDL-cholesterol [aOR, 0.68; 95% CI: 0.46–0.99; P = 0.048] and apolipoprotein B [aOR, 0.64; 95% CI: 0.44–0.92; P = 0.016] lipid targets.

Conclusions: Diabetic women were less likely to be on optimal hypolipemic therapy and consequently less likely to attain lipid goals compared to men. This shows a sex gap on dyslipidemia treatment in the region. Diabetic women with very high ASCVD risk status need to be aggressively treated to lower their risk of cardiovascular events.

Keywords: Cardiovascular disease, Low density lipoprotein cholesterol, Apolipoprotein B, Sex, Arabs, Middle East

Background

Type 2 diabetes mellitus is a global public health issue that affects around 8.5% of adult population according to the World Health Organization [1]. This problem is particularly alarming in the Middle East region where the average prevalence is more than twice (14.8–20%) of Western countries [2]. The prevalence of atherosclerotic cardiovascular disease (ASCVD) and its associated morbidity and mortality are substantially higher among diabetics than non-diabetics [3]. Furthermore, women with diabetes have considerably higher risk of coronary heart disease (CHD) mortality compared to men, even after adjusting for confounding factors [4, 5].

Dyslipidemia management is an important prevention strategy to reduce cardiovascular risk in both sexes [6–9]. However, despite equitable access to lipid lowering therapy, cardiovascular disease studies
have shown that women are less likely to attain their optimal lipid goals as compared to men [10–17].

Despite the high prevalence of dyslipidemia [18] and diabetes [2] in the Arabian Gulf region, there are currently limited data assessing sex disparity gaps in management and outcomes of dyslipidemia among diabetics in this region. Hence, the objective of this study was to determine sex differences in management and outcomes among diabetic patients in the Arabian Gulf.

Methods

The details of this study have been previously described [19]. Briefly, the CEPHEUS study was a multi-center non-interventional survey of patients on lipid lowering drugs (LLDs) in six Arabian Gulf countries (Saudi Arabia, United Arab Emirates, Oman, Qatar, Bahrain and Kuwait). A total of 5457 patients were enrolled in this survey from outpatient clinics by 177 specialists and primary care physicians. However, this sub study included only those that were diabetic (n = 3336) and had non-missing information on sex. The study was conducted between November 2009 and July 2010. The inclusion criteria were: patients ≥18 years of age taking LLDs for ≥3 months and with no dose change for a minimum of 6 weeks.

A fasting blood sample was taken from each subject for measurement of total cholesterol (TC), high-density lipoprotein cholesterol (HDLC), low-density lipoprotein cholesterol (LDLC), triglycerides (TG), apolipoprotein B (ApoB), glucose and glycated hemoglobin A1c (Hba1c).

All blood samples were tested at the King Faisal specialist Hospital and Research Centre (Riyadh, Saudi Arabia). All laboratory tests underwent internal and external quality control checks.

Study subjects were checked for statin use, type, and specifically the use of high doses of atorvastatin (40–80 mg) and rosuvastatin (20–40 mg). Statin combination was defined as statin prescription along with the addition of other LLDs. Other LLDs included fibrates (benzafibrate, fenofibrate, gemfibrozil), bile acid sequestrant (colestipol) and ezetimibe.

Criteria for ASCVD risk status was derived from the National Lipid Association (NLA) recommendations for patient-centered management of dyslipidemia Part 1–Executive Summary [20]. High-risk group included diabetic patients (type 1 or 2) with 0/1 other major ASCVD risk factor or LDL-C ≥ 5.02 mmol/L (190 mg/dL; severe hypercholesterolemia). The very high-risk group included ASCVD or diabetes mellitus with ≥2 other major ASCVD risk factors. Low HDLC was defined as levels of 1.0 mmol/L (< 40 mg/dL) for men and 1.3 mmol/L (< 50 mg/dL) for women. Therapeutic lipoprotein targets for the high-risk patients were LDL-C < 2.6 mmol/L (100 mg/dL), ApoB < 0.90 g/L and non-HDL-C < 3.3 mmol/L (130 mg/dL). For the highest risk group, therapeutic lipoprotein targets were LDL-C < 1.8 mmol/L (70 mg/dL), ApoB < 0.80 g/L and non-HDL-C < 2.6 mmol/L (100 mg/dL) [20].

Statistical analysis

For categorical variables, frequencies and percentages were reported and differences between groups were analyzed using Pearson’s χ² tests (or Fisher’s exact tests for cells < 5). For continuous variables, mean and standard deviation were used to summarize the data. Analyses were performed using Student’s t-tests. The association between LDL-C, non-HDL-C and ApoB goal attainment and sex was evaluated using multivariate logistic regression models adjusted for age, body mass index (BMI), smoking status, metabolic syndrome, baseline TG and LDL-C as well as statins prescribed (simvastatin or atorvastatin and rosuvastatin) and the associated dose strengths of the latter. The goodness-of-fit of the logistic model was examined using the Hosmer and Lemeshow goodness-of-fit statistic [21]. The Hosmer and Lemeshow test analyses the actual versus the predicted responses; theoretically, the observed and expected counts should be close. Based on the χ² [2] distribution, a Hosmer and Lemeshow statistic with a P > 0.05 is considered a good fit. An a priori two-tailed level of significance was set at 0.05. Statistical analysis was carried out using STATA version 13.1 (STATA Corporation, College Station, TX, USA).

Results

Table 1 shows demographic and clinical characteristics of the whole cohort and according to sex. The overall mean age was 57 ± 11 years and 45% (n = 1486) were females. The average BMI was 32 kg/m² and 55% (n = 1843) were obese. The proportion of patients with coronary heart disease, metabolic syndrome and hypertension were 30% (n = 999), 76% (n = 2437) and 70% (n = 2330), respectively. Most patients (83%; n = 2755) had very high ASCVD risk status. The majority (95%; n = 3160) was on statin monotherapy. Patients on statin combination and other LLDs constituted only 4.4% (n = 145) and 0.9% (n = 31), respectively.

Table 1 also shows that females had a greater prevalence of obesity (P < 0.001) and the metabolic syndrome (P < 0.001). They also had higher TC (P < 0.001), LDL-C (P < 0.001), non-HDL-C (P = 0.001) and ApoB (P < 0.001) concentrations. On the other hand, males had a greater prevalence of smoking (P < 0.001), coronary heart (P < 0.001), peripheral (P = 0.042) and cerebrovascular (P = 0.004) diseases. Of importance, every 3 in 4 women were considered as being at very high ASCVD risk, however this prevalence was higher in men (roughly 9 in 10 individuals, P < 0.001).

As shown in Fig. 1, when compared to males, females at highest ASCVD risk category had a greater proportion
of low HDL-C levels (35% vs 47%; \(P < 0.001\)) and achieved less LDL-C (21% vs 30%; \(P < 0.001\)), non-HDL-C (34% vs 38%; \(P = 0.034\)) and ApoB (34% vs 40%; \(P = 0.002\)) goals. Figure 2 shows that females at the high ASCVD risk category, apart from lower HDL-C (68% vs 86%; \(P < 0.001\)) levels, there were no significant differences in lipid target achievements.

Table 1 shows that women were more likely to be on statin monotherapy compared to men (\(P < 0.001\)). However, they were less likely to be on more efficacious lipid lowering therapies like atorvastatin (41% vs 46%; \(P < 0.001\)) and rosvastatin (7.2% vs 11%; \(P < 0.001\)) than males. On the same token, females with very high ASCVD risk status were less likely to be associated with use of high doses of atorvastatin (40 and 80 mg) compared to males (23% vs 29%; \(P = 0.035\)); however, no significant differences were noted regarding the use of 20 and 40 mg doses of rosvastatin (combined) (39% vs 31%; \(P = 0.211\)).

In those with high ASCVD risk status, no differences were noted between the sexes regarding the use of high doses of both atorvastatin (10% vs 11%; \(P = 0.968\)) and rosvastatin (38% vs 13%; \(P = 0.154\); power = 24%). On the contrary, female sex was associated with a greater use of simvastatin (51% vs 41%; \(P < 0.001\)). Furthermore,
females were also less likely to be prescribed statin drug combination (2.8% vs 5.6%; \( P < 0.001 \)) and other LLDs (0.4% vs 1.4%; \( P = 0.005 \)).

Table 2 shows the association between LDL-C, non-HDL-C and ApoB goal attainment and sex using multivariate logistic regression models adjusting for confounders. The results indicated that females with very high ASCVD risk were less likely to achieve LDL-C [adjusted odds ratio (aOR), 0.58; 95% confidence interval (CI): 0.40–0.86; \( P = 0.006 \)], non-HDL-C [aOR, 0.68; 95% CI: 0.46–0.99; \( P = 0.048 \)] and ApoB [aOR, 0.64; 95% CI: 0.44–0.92; \( P = 0.016 \)] goal attainments. Of note, high TGs were also inversely associated with non-HDL-C [aOR, 0.16; 95% CI: 0.11–0.24; \( P < 0.001 \)] and ApoB [aOR, 0.30; 95% CI: 0.22–0.41; \( P < 0.001 \)] goal attainments. Of interest, simvastatin use in diabetics with very high ASCVD was also inversely associated with LDL-C [aOR, 0.49; 95% CI: 0.32–0.75;
The associations between LDL-C, non-HDL-C and Apo B goal attainment and sex, in diabetics with very high ASCVD risk status, adjusting for various other factors in the models, were performed using multivariate logistic regressions.

| Characteristic | LDL-C goal | Non-HDL-C goal | Apo B goal |
|---------------|------------|----------------|------------|
|               | aOR[95% CI] | P-value        | aOR[95% CI] | P-value        | aOR[95% CI] | P-value |
| Female        | 0.58 [0.40–0.86] | 0.006 | 0.68 [0.46–0.99] | 0.048 | 0.64 [0.44–0.92] | 0.016 |
| Age           | 1.01 [0.98–1.03] | 0.217 | 1.01 [0.99–1.02] | 0.558 | 1.00 [0.99–1.02] | 0.587 |
| BMI           | 1.00 [0.97–1.03] | 0.734 | 1.00 [0.97–1.03] | 0.984 | 1.00 [0.97–1.02] | 0.860 |
| Smoker        | 0.68 [0.41–1.12] | 0.127 | 0.78 [0.47–1.30] | 0.342 | 0.70 [0.43–1.13] | 0.142 |
| MetS          | 0.84 [0.57–1.23] | 0.371 | 1.59 [1.06–2.39] | 0.026 | 1.15 [0.78–1.68] | 0.474 |
| TG            | 0.86 [0.71–1.04] | 0.127 | 0.16 [0.11–0.24] | < 0.001 | 0.30 [0.22–0.41] | < 0.001 |
| LDL-C         | 1.00 [1.00–1.00] | 0.857 | 1.00 [1.00–1.00] | 0.420 | 1.00 [1.00–1.00] | 0.127 |
| Simvastatin   | 0.49 [0.32–0.75] | 0.001 | 0.55 [0.37–0.83] | 0.004 | 0.53 [0.37–0.78] | 0.001 |
| Statin dose   | 1.00 [1.00–1.00] | 0.251 | 1.00 [1.00–1.00] | 0.548 | 1.00 [1.00–1.01] | 0.204 |

LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol; Apo B, apolipoprotein B; ASCVD, atherosclerotic vascular disease; aOR, adjusted odds ratio; CI, confidence interval; BMI, body mass index; MetS, metabolic syndrome; TG, triglycerides

Although women with diabetes mellitus have an increased risk of cardiovascular morbidity and mortality compared with diabetic men [4, 5], the present study revealed that women were undertreated and less likely to attain the recommended lipid and ApoB goals than their male counterparts. Similar findings have been reported elsewhere [12, 22, 23].

The reasons for the gender disparity in the management of dyslipidemia are not totally clear. However, several possible explanations have been put forward. It’s reported that, in general, women are less concerned about their health and may not raise their symptoms with their physicians [24]. Goldberg et al. also reported that women may experience CVD symptoms that are atypical and different from those of men and hence may not discuss their encounters with their physicians and consequently their CVD symptoms may not be further evaluated [25]. Physicians have also been reported to perceive women at lower risk than men despite having similar CHD risk equivalents [26].

This study has also demonstrated that lipid treatment goals, especially for those with diabetes and very high ASCVD risk status, are significantly lower in females compared to males. These findings are consistent with previous studies [10–17]. In an earlier published study from the CEPHEUS project, it also documented that women were less likely to attain their lipid target achievements in high and very high ASCVD risk patients in the Arabian Gulf [10]. However, the current study aimed to look at gender disparity only in dyslipidemia management and lipid outcomes in the diabetic population with CHD. Gender differences in lipid goal attainment rates between men and women have been explained by differences in socioeconomic status, cardiovascular co-morbidities and associated risk factors, baseline lipid...
level, and the dosage of statin treatment [15]. In the Lipid Treatment Assessment Panel-2 study (LTAP-2), diabetes, hypertension and the presence of the metabolic syndrome were associated with a greater chance of failing LDL-C goal success in women, while in men it was only diabetes [12]. Gene-gender interactions may also contributed to gender disparities in lipid goal attainment [27]. For example, an apolipoprotein E (ApoE) polymorphism, in respect to statin therapy, has been found to be different between men and women [28].

In a review paper by Banach and colleagues [29], they concluded that statin non-adherence may be the main cause of inadequate LDL-C reduction. Statin associated muscle symptoms have been reported to be the most common cause of statin discontinuation or dose reduction [30]. In a metanalysis on gender and racial disparities to statin therapy, Lewey et al. [31] reported that women and non-white patients were at an increased risk for non-adherence to statin medication. However, in this diabetic cohort based on survey questions (‘I always take my medication to lower cholesterol every day’), there were no significant differences in adherence to statin medication between males and females (87% vs 89%; \( P = 0.221 \)).

In this study, in the very high ASCVD category, most men and women were not in use of elevated doses of potent statins and lipid lowering drug associations however; this finding was more frequent in the latter. On the same token, women were more frequently receiving simvastatin, a less efficacious statin, compared to men who were receiving more potent atorvastatin and rosuvastatin. Indeed, the use of simvastatin was independently associated with a greater adjusted odds of failing to attain not only LDL-C but also non-HDL-C and ApoB goals at the very high ASCVD risk group.

Our findings provide a useful overview of dyslipidemia management and treatment outcomes in ASCVD diabetic patients stratified by gender in the Middle East. However, the study is not without limitations, it is an observational cross-sectional trial that captured only a snapshot of variables at a point in time and did not assess long-term outcomes. Missingness of important variables like statin doses, anti-diabetic and anti-hypertensive medications including diuretics as well as baseline lipid levels, which could have affected levels and consequently outcomes, is a limitation. The population studied was relatively small and considerable variability in practice patterns across the Arabian Gulf exists, and probably even among study sites, and therefore caution should be exercised when extrapolating the results to the general population.

**Conclusion**

This study has demonstrated that diabetic women with ASCVD were less likely to be on optimal lipid lowering therapy compared to men and therefore to attain lipid goals proposed to prevent cardiovascular events. This clearly shows a sex gap on lipid management in the region that needs to be reduced with urgency considering the elevated prevalence of diabetes in the region and the high risk of cardiovascular and complications and mortality that diabetic women bear. Diabetic women with very high ASCVD risk status need to be aggressively treated to lower their risk of cardiovascular events.

**Abbreviations**

AOR: Adjusted odds ratio; ApoB: Apolipoprotein B; ApoE: Apolipoprotein e; ASCVD: Atherosclerotic cardiovascular disease; BMI: Body mass index; CEPHEUS: Centralized pan-middle-east survey; CHD: Coronary heart disease; CI: Confidence interval; CVD: Cardiovascular disease; Hba1c: Glycated hemoglobin a1c; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; LLDs: Lipid lowering drugs; LTAP-2: study Lipid treatment assessment panel-2 study; NLA: National lipid association; TC: Total cholesterol; TG: Triglycerides

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**Availability of data and materials**

All data generated or analyzed during this study are included within the article.

**Authors’ contributions**

All authors were in charge of the study design, questionnaire design, and quality control; All authors, except IA, FA and RDS, were in charge of the field investigation, quality control, and data arrangement; IA was in charge of data arrangement, analysis, and paper writing. All authors read and approved the final manuscript for publication.

**Ethics approval and consent to participate**

This study complied with the Declaration of Helsinki. The study had approval from the internal review bodies/ethics committees of each participating institution in the each of the Arabian Gulf countries. Informed written consent was obtained from all patients enrolled in the study.

**Consent for publication**

Not applicable.

**Competing interests**

RDS has received honoraria related to consulting, research and or speaker activities from: Amgen, Astra Zeneca, Biolab, Boehringer-Ingelheim, Eli-Lilly, Kowa, Merck, Pfizer, Sanofi/Regeneron and Procaps. The other authors disclose that they have no significant relationships with or financial interests in any commercial companies related to this study or article.

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