Increased cholesterol intake in women with gestational diabetes mellitus

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Abstract

Aim. – Cholesterol intake is associated with the risk for type 2 diabetes mellitus, but no previous studies have evaluated its role regarding the risk of gestational diabetes mellitus (GDM). We investigate the relation between cholesterol intake and GDM.

Methods. – At screening for GDM, 335 pregnant women were evaluated for dietary intake (including cholesterol) during the previous year (validated food-frequency questionnaire).

Results. – Forty-one women were diagnosed with GDM and 294 did not meet the GDM criteria. Women with GDM were older (32.8 ± 0.7 vs. 30.2 ± 0.3 years; \(P = 0.01\)) and had a higher body mass index (27.3 ± 0.7 vs. 24.3 ± 0.3 kg/m²; \(P = 0.01\)) than women without GDM. They also had more frequently a family history of type 2 diabetes mellitus (51.2% vs. 40.0%; \(P = 0.02\)) and history of previous GDM (14.6% vs. 1.7%; \(P = 0.01\)), and were evaluated earlier in pregnancy (22.1 ± 1.2 vs. 24.9 ± 0.5 weeks; \(P = 0.03\)). There were no significant differences between groups in smoking habit, and alcohol, total energy, protein, carbohydrate, fats and fiber intake. Women with GDM had a higher cholesterol intake than women without GDM (145.3 ± 4.5 mg/1000 kcal vs. 134.5 ± 1.6 mg/1000 kcal; \(P = 0.03\)). In a multiple logistic regression model, previous GDM, BMI, age and cholesterol intake (OR = 1.88; 95% CI: 1.09 – 3.23 for each increase of 50 mg/1000 kcal) were independently and positively associated with GDM.

Conclusion. – We conclude that cholesterol intake is independently associated with GDM and that it could be involved in the pathogenesis of GDM.

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Conclusions. – Les apports alimentaires en cholestérol sont associés de manière indépendante au risque de survenue d’un DG, et pourraient être impliqués dans la pathogénie de celui-ci.
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Mots clés : Apports alimentaires en cholestérol ; Diabète gestationnel ; Régime méditerranéen ; Apports alimentaires en lipides

1. Introduction

Diet is one of the most important factors associated with the development of type 2 diabetes mellitus. The dietary fat more consistently associated with an increase in the risk of type 2 diabetes mellitus is saturated fat [1–3]. This conclusion has recently been supported by the results of two randomized controlled clinical trials on the prevention of type 2 diabetes mellitus [4,5]. Additionally, low polyunsaturated fat intake, high trans unsaturated fat intake, and high cholesterol intake have all been associated with an increased risk of type 2 diabetes mellitus too [3]. Several previous studies have reported an association between high intake of cholesterol and the risk of type 2 diabetes mellitus [6–9]. Nevertheless, as cholesterol is only present in products from animal origin, the general view is that this association should be attributed to other components of animal products associated to cholesterol, like saturated fat [3].

Diets in the Mediterranean area have a relatively high fat content, which is achieved by a low content of saturated fat and a high content of monounsaturated fat [10,11]. In these diets, cholesterol intake is not so tightly associated with the intake of saturated fat as in the typical Western diet. Therefore, the study with subjects on a Mediterranean diet may provide the opportunity to evaluate the possible association between cholesterol intake and diabetes risk reducing the confounding effect of saturated fat intake.

Type 2 diabetes mellitus and gestational diabetes mellitus (GDM) share similar risk factors and pathophysiological mechanisms. In fact, women with GDM are at an increased risk of developing type 2 diabetes mellitus [12]. Although diet therapy is a cornerstone of the treatment of GDM, there are few studies relating to the association between dietary intake and glycemic status during pregnancy [13–16]. None of these studies reported cholesterol dietary intake during pregnancy. Our study was aimed at investigating the relationship between cholesterol intake and the risk of GDM in a cohort of Caucasian pregnant women on a Mediterranean diet.

2. Materials and methods

2.1. Subjects

All subjects were pregnant women consecutively referred for screening of GDM from one of the Primary Health Care districts attended to by the Department of Diabetes, Endocrinology and Nutrition at the Hospital de Sabadell from February 1st, 2001 to February 1st, 2002. Screening and diagnosis of GDM were performed according to the guidelines from the “Third International Workshop Conference on GDM” [17]. Pregnant women known to have diabetes mellitus or a disease affecting glucose metabolism were excluded. According to the recommendation of the Regional Public Health Authority, all pregnant women received a glucose challenge test (GCT) from weeks 24 to 28 of gestation, without any selection from individual obstetricians. However, the obstetrician could request the GCT between weeks 14 and 18 of gestation, when risk factors were present: family history of diabetes, age ≥35 years, pre-pregnancy overweight, personal history of GDM, previous macrosomia or glycosuria. In this latter group, when the GCT result was negative, a further GCT was performed between weeks 24 and 28 of gestation. The GCT consisted of a standard 50-g glucose load performed after an overnight fast. In this test, plasma glucose concentration (glucose oxidase method) was measured 1 hour after the load and a value of ≥7.8 mmol/l was considered positive according to recommendations from the Fourth International/Workshop Conference on GDM. A GCT glucose value of ≥11.1 mmol/l was considered diagnostic of GDM. In all women with a positive GCT, a 3-hour oral glucose tolerance test (100 g) was performed within 1–2 weeks after the initial GCT. The OGTT was carried out and evaluated according to the recommendations from the National Diabetes Data Group [18]. All participants gave their informed consent and all the procedures were approved by the Local Ethics Committee.

2.2. Variables evaluated

Each woman was evaluated at screening, before knowing the results of the GCT. The following variables were recorded: age; pre-pregnancy body weight; height; BMI (calculated as pre-pregnancy weight in kilograms divided by the square of the height in meters); previous history of pregnancies and GDM; family history of type 2 diabetes mellitus (first-degree relative as diagnosed by a physician); current smoking status; gestational age; usual dietary intake during the previous year.

To evaluate the dietary intake, we used a validated semi-quantitative food-frequency questionnaire, including 93 different kinds of food and beverages commonly consumed in Spain. This questionnaire is the Spanish equivalent of the Harvard Questionnaire [19] which was modified and validated for the Mediterranean area of Spain [20]. The questionnaire is specifically extended to fully cover the kinds of vegetables and fruit consumed by the Spanish population [21,22]. Each questionnaire was personally administrated by a registered nurse specialized in the management of diabetes and blinded for the gly-
Nineteen of the possible responses for each food item were considered: dairy products; eggs; meat; fish; vegetables; legumes; fruit; potatoes; cereals; oils, butter and margarines; sugar and sweets; and alcoholic and non-alcoholic beverages, and precooked dishes. We computed nutrient intakes by multiplying the consumption frequency of each food with the nutrient content in the specified portion. The software Food Processor Plus version 6 was used to convert the consumption frequencies to nutrients, as previously described in [23].

### 2.3. Statistical analyses

Data are presented as mean ± S.E.M. or as percentages. Group frequencies were compared using the $\chi^2$ or Fisher’s exact test where appropriate. Differences between group means were tested using the t-test to improve skewness and kurtosis of the distributions, those variables not normally distributed, were logarithmically transformed for statistical analyses and then back-transformed to their natural units for presentation in tables. The associations between saturated fat, monounsaturated fat and cholesterol intake were investigated by calculating the Pearson’s correlation coefficient. A multiple logistic model based on the maximum-likelihood method with GDM as the dependent variable, was used to adjust dietary intake for other known risk factors for GDM such as age, BMI, family history of diabetes mellitus or previous GDM. All $P$ values were two-sided and a $P$ value $\leq 0.05$ was considered statistically significant. The statistical analysis was performed with the SPSS statistical package, version 11.5 (Chicago, IL).

### 3. Results

A total of 335 Caucasian women were evaluated: 41 women with and 294 without GDM. Of these 335 women, 93 were evaluated between the 14th and the 18th week of pregnancy and the rest between the 18th and the 28th week. Of the 41 women who were diagnosed with GDM, 16 received their diagnosis of GDM between the 14th and the 18th week of pregnancy, although only four had a basal plasma glucose higher than 100 mg/dl and none equal or higher than 126 mg/dl.

Table 1 shows the clinical characteristics of all the subjects evaluated. Women with GDM were older, shorter and had a higher pre-pregnancy weight and BMI. In addition, they more frequently had a previous history of GDM and type 2 diabetes mellitus in first-degree relatives. They were evaluated earlier during pregnancy than women without GDM. No significant differences were found in relation to parity and smoking habits.

Table 2 shows the nutritional data obtained from the semi-quantitative food-frequency questionnaire. There were no significant differences between the two groups regarding alcohol intake, total energy and fat, protein and carbohydrate intake, expressed as a percentage of total energy and complex carbohydrates expressed as a percentage of total carbohydrates. No significant differences in terms of saturated fat, polyunsaturated fat and monounsaturated fat intake were found (all measured as total kcal % or as total fat %) (Table 2). Moreover, there were no differences in the polyunsaturated:saturated fat ratio between the two groups. Notably, women with GDM had a significantly higher intake of cholesterol than women without GDM (145.3 ± 4.5 mg/1000 kcal vs. 134.5 ± 1.6; $P = 0.03$). The intake of fiber and trans unsaturated fat showed no differences in the two groups (Table 2). In the overall group, the Pearson’s coefficient of correlation between cholesterol and saturated fat (measured as total kcal %) was 0.33 ($P < 0.001$).

In a multiple logistic regression model, the following variables were initially entered: BMI, family history of type 2 diabetes mellitus and previous GDM. The following variables were entered as independent variables: age, height, weight, pre-pregnancy BMI, weeks of pregnancy, parity, smoking status, family history of diabetes mellitus, previous GDM, previous GDM, type 2 diabetes mellitus, parity, and smoking status. The following variables were entered as independent variables: age, height, weight, pre-pregnancy BMI, weeks of pregnancy, parity, smoking status, family history of diabetes mellitus, previous GDM, type 2 diabetes mellitus, parity, and smoking status. The following variables were entered as independent variables: age, height, weight, pre-pregnancy BMI, weeks of pregnancy, parity, smoking status, family history of diabetes mellitus, previous GDM, type 2 diabetes mellitus, parity, and smoking status.
Table 3
Multiple logistic regression analysis evaluating the association of gestational diabetes (dependent variable) with the following variables: age, BMI before pregnancy, family history of type 2 diabetes mellitus, previous GDM, protein intake (% total calorie intake), carbohydrate intake (% total calorie intake), fat intake (% total calorie intake), saturated, monounsaturated and polyunsaturated fat intake (% total calorie intake), fiber intake (g/1000 kcal), cholesterol intake (g/1000 kcal), and trans unsaturated fat (% total fat intake)

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous GDM (^a^)</td>
<td>8.18 (2.13–31.47)</td>
<td>0.002</td>
</tr>
<tr>
<td>Age (^b^)</td>
<td>1.12 (1.04–1.21)</td>
<td>0.003</td>
</tr>
<tr>
<td>BMI (^c^)</td>
<td>1.09 (1.02–1.17)</td>
<td>0.015</td>
</tr>
<tr>
<td>Cholesterol intake (^d^)</td>
<td>1.88 (1.09–3.23)</td>
<td>0.024</td>
</tr>
</tbody>
</table>

\(^a^\) Absence versus presence of previous gestational diabetes.
\(^b^\) For each 1 year increase.
\(^c^\) For each kg/m\(^2^\) increase.
\(^d^\) For each 50 mg/1000 kcal increase of cholesterol intake.

Discussion

In the current study, we found that a high cholesterol intake was the only dietary factor associated with the diagnosis of GDM in a group of pregnant women on a Mediterranean diet (rich in monounsaturated fat), after controlling for GDM risk known factors. It is estimated that an increase of 50 mg of cholesterol/1000 kcal is associated with a mean increase of 88% in the risk of GDM. We did not find any relationship between the presence of GDM and the intake of saturated, monounsaturated, polyunsaturated or trans unsaturated fat.

No previous studies examined the possible association of cholesterol intake during pregnancy and GDM. However, type 2 diabetes mellitus shares most risk factors with GDM, and some prospective studies found a positive association between cholesterol intake and type 2 diabetes mellitus. Feitkens et al. [7] found a positive correlation between dietary cholesterol and the 20-year diabetes incidence in the Finnish and Dutch cohorts of the Seven Countries Study. This finding supported the results of a previous cross-sectional study on the Dutch cohort [6]. More recently, the association between dietary cholesterol intake and diabetes risk was confirmed in the Nurses’ Health Study [8]. In this study, a low polyunsaturated fat intake and a high trans unsaturated fat intake were also associated with type 2 diabetes mellitus. Additionally, a positive relation between cholesterol intake and type 2 diabetes mellitus was shown in the Iowa Women’s Health Study, although in this case diabetes risk was also positively associated with saturated fat intake [9]. As anticipated, in our study the positive correlation between cholesterol intake and saturated fat intake was lower than in the Iowa Women’s Health Study. Because of this, the possible confounding role of saturated fat in our study was reduced. However, despite this we also found an association between cholesterol intake and the risk of GDM. This finding would support a role of cholesterol intake in the diabetes risk, regardless of the intake of other fat components. It is unclear how dietary cholesterol may affect diabetes incidence. As cholesterol is only present in products of animal origin, it has been speculated that these associations could represent an adverse effect of a food pattern characterized by a high consumption of meat and eggs, or even an unidentified component of animal products. Regarding this, the association between processed meat intake and the incidence of diabetes found in the Health Professionals Follow-up Study is of interest [24]. However, a direct effect of cholesterol intake on the incidence of diabetes could not be ruled out. Inflammatory mechanisms have recently been implicated in the development of type 2 diabetes mellitus [25]. In animal models, cholesterol itself can stimulate inflammatory pathways [26] and dietary cholesterol intake per se produces an increase in serum amyloid A protein, a serum inflammatory marker [27]. Additionally, a recent study showed that decreasing serum cholesterol levels with pravastatin is associated with a decrease in the incidence of type 2 diabetes mellitus [28]. Although pleiotropic effects of statins could be responsible for this preventive effect, it is possible that the cholesterol lowering effect of statin per se could be partially responsible for this effect.

In our study, no relationship between GDM and the intake of saturated, monounsaturated, polyunsaturated or trans unsaturated fat was found. Few previous observational studies investigated the association between dietary intake and GDM. Recently, Saldana et al. [13], in a cohort of 1698 pregnant women from North Carolina, found an association between increased fat intake and the development of glucose abnormalities during pregnancy. However, they did not evaluate the different types of fat in the diet. Moses et al. [14] assessed the relationship between the recurrence of GDM and dietary intake and also found that a higher fat intake was associated with a recurrence of GDM. In a case–control study in 171 nulliparous Chinese women, Wang et al. [15] found a lower intake of polyunsaturated fat in women with GDM. An additional study in a group of 504 north Italian pregnant women, found that those with GDM had a higher intake of saturated fat [16]. These findings are in agreement with the results of some of the above-mentioned epidemiological studies on dietary intake and risk of type 2 diabetes [7–9]. However, these two latter studies [15,16] differ significantly from our study in the dietary intake composition of the women evaluated (intake of carbohydrates, fat and type of fat). In fact, the dietary intake composition in our study was closer to a Mediterranean diet than in these two previous studies.

Several limitations of the present study deserve mentioning. Firstly, as a cross-sectional study, the results presented only indicated an association between cholesterol intake and GDM in our population. However, this study cannot address causation. In this setting, residual confounding by incomplete control for other dietary factors remains an alternative explanation.
Secondly, dietary interviews have some obvious limitations. We relied on self-reported intake data from free-living people. It is well known that dietary self-reported data tends to underestimate total intakes, and food records may not represent typical intake patterns. However, because most of these women were buying and cooking food for themselves and for their families, their information would be the best and most accurate regarding portions, amounts and kinds of condiments served. Finally, another limitation in our study was the lack of any measure of physical activity. In obese pregnant women, it has been described that a higher percentage of physically inactive subjects have GDM [29]. However, Bo et al. [16] did not find any relation between physical activity and glycemic status.

In conclusion, the current data show that in pregnant women on a Mediterranean diet, a higher intake of cholesterol is associated with GDM. Further studies are warranted to confirm the association between higher cholesterol intake and GDM and before designing clinical trials to prevent GDM in women at high risk for GDM, through a decrease in cholesterol intake during pregnancy.

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