Effect of dietary calcium intake on weight gain in type 2 diabetic patients following initiation of insulin therapy

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SUMMARY

Objectives: This pilot study analyses weight gain in type 2 diabetic patients at initiation of insulin therapy, according to daily calcium intake.

Methods: Type 2 diabetic patients consecutively admitted for initiation of insulin therapy were studied between January and March 2004 in a monocenter study. Dietary intake was assessed by a 7-day food history before insulin treatment (initial visit) and 4 to 6 months later (final visit).

Results: Thirty-one patients were studied (18 males and 13 females; mean age 62±9 years, with diabetes duration 14±10 years). Weight significantly increased between initial and final visits (81.9±16.2 vs. 84.8±17.8 kg; P=0.0272). Median weight gain was 2.4 kg (IQR: -1.15 to +5.27 kg). Waist circumference increased by 2 cm (IQR: 0 to +4 cm). There was no difference between weight change and tertile of calcium intake adjusted on energy intake. We did not find any correlation between weight change and tertile of calcium intake adjusted on energy intake. We did not find any correlation between waist circumference change and tertile of calcium intake (R=0.324; P=0.1205) or dairy calcium intake (R=0.285; P=0.0755).

Conclusion: We found no relation between total or dairy calcium intake and weight change during initiation of insulin therapy in type 2 diabetic patients. Dietary calcium intake does probably not play a major role on insulin-induced body weight gain.

Key-words: Calcium intake · Dairy products · Weight · Insulin therapy · Type 2 diabetes.

RéSUMÉ

Influence des apports alimentaires en calcium sur la prise de poids observée chez les diabétiques de type 2 après mise à l’insuline

Objectif: Cette étude pilote analyse la prise pondérale à la mise en route d’un traitement insulinique chez des sujets diabétiques de type 2, en fonction de l’apport calcique.

Méthodes: Des patients diabétiques de type 2 admis pour mise à l’insuline entre janvier et mars 2004 ont été étudiés dans une étude mono-centrique. Les apports alimentaires étaient estimés par l’interrogatoire alimentaire sur 7 jours, avant le début (visite initiale) et 4 à 6 mois plus tard (visite finale).

Résultats: 31 sujets ont été étudiés (18 hommes et 13 femmes ; age moyen : 62 ± 9 ans et durée connue de diabète 14 ± 10 ans). Le poids a augmenté significativement entre la visite initiale et la visite finale : 81.9 ± 16.2 vs 84.8 ± 17.8 Kg ; P = 0,0272). La prise de poids médiane était de 2 Kg (IQR : -1,15 à 5,27). La médiane de tour de taille a augmenté de 2 cm (IQR : 0 à 4). Il n’y avait pas de différence de prise de poids en fonction du tertile d’apport calcique/apport énergétique. Nous n’avons pas noté de relation entre la prise de poids et l’apport calcique total (R = 0.186 ; P = 0,3165), ni l’apport en calcium laitier (R = 0,191 ; P = 0,3040). De même, nous n’avons pas noté de relation entre la modification du tour de taille et l’apport calcique total (R = 0,324 ; P = 0,1205), ni l’apport en calcium laitier (R = 0,285 ; P = 0,0755).

Conclusion: Nous n’avons trouvé aucune relation entre l’apport calcique total ou en calcium laitier et les modifications de poids à la mise en route d’une insulinothérapie chez des patients diabétiques de type 2. L’apport calcique ne joue probablement pas de rôle majeur dans la prise de poids induite par l’insuline.

Mots-clés : Apport calcaire · Calcium laitier · Poids · Insulinothérapie · Diabète de type 2.
Introduction

Obesity is recognized as a major public health issue worldwide [1]. Hypertension, diabetes mellitus and dyslipidemia are more frequent in obese patients and mortality is increased compared with normal weight subjects [2,3]. Recent studies have shown that calcium intake is inversely related to BMI and risk of obesity [4-6]. Post-hoc analysis of data regarding body weight in osteoporosis trials have shown a significant inverse correlation between calcium intake and BMI; an increment of 1000 mg calcium intake was related to a 8 kg decrement of body weight [7]. In a secondary analysis of an exercise intervention trial, the authors found significant inverse correlations between calcium intake and change in body weight and body fat mass after a two-year period of observation [8]. Two studies have reported a beneficial effect of milk consumption on weight reduction [9,10]. Several studies have shown that only dairy calcium had an effect on weight loss [8,11]. In all of these studies, diabetic patients were systematically excluded.

In type 2 diabetic subjects, obesity is very common. Weight gain is a frequent side effect of insulin therapy in these patients. Studies reported an average weight gain of 6 kg, corresponding with 6% of initial body weight in the first months of treatment onset [12]. In the UKPDS study, weight gain was greater in the intensively treated group (mean 2.9 kg) than in the conventionally-treated group of type 2 diabetic patients [13], and others reported that a decrease in HbA1c by 1% was associated with a 2 kg weight gain [14]. Insulin therapy leads to an increase in both fat and fat-free-mass [15,16]. In patients on insulin alone, there is a greater deposition of trunkal fat compared with patients on combination therapy [16]. Increasing dietary calcium has been shown to accelerate weight and fat loss in mice [17] and humans [11], and to shift the distribution of fat loss leading to a greater abdominal fat loss on a high calcium diet [11].

To our knowledge, no study was performed in diabetic patients to date. However, knowing if calcium intake influences weight gain in diabetic patients newly treated with insulin could strongly influence our dietary advice in these patients.

The aim of our pilot study was to compare weight gain in type 2 diabetic patients after initiation of insulin therapy according to daily calcium intake with special emphasis on dairy calcium or total calcium intake.

Patients and methods

Patients

Type 2 diabetic patients domiciled in the Poitiers urban area, in whom insulin treatment was initiated due to failure of oral anti-diabetic agents, were consecutively included between January and March 2004 in our center.

Type 2 diabetes was defined according to the ADA classification [18] using the following criteria: age at onset >40 years, no urinary ketosis at diagnosis and no need for continuous insulin treatment for more than two years, after diabetes onset.

The exclusion criteria were vegetarian and vegetalian patients, patients treated with calcium and/or vitamin D, patients with food behavioural problem (anorexia nervosa and binge-eating disorder and/or bulimia) recorded by medical and dietary history.

Procedure

At baseline, patients were admitted to the diabetes clinic for education to insulin injection (initial visit). They were re-examined in out-patient visit by a physician unaware of baseline calcium intake, and by a dietetician 4 to 6 months later (final visit).

In both visits, patients were examined and asked about their physical activity, tobacco use and treatment. Blood samples were collected to analyse fasting plasma glucose, HbA1c, total cholesterol, HDL cholesterol and triglycerides.

Dietary calcium intake considered for analyses was the mean of the estimation of 7-day food history at initial and final visits.

Diet history

Dietary intake was assessed by 7-day food history by a trained dietetician before insulin treatment and 4 to 6 months later. Data were coded using the Profil ®-ACIM (Saint Doulchard, France) with the REGAL nutrient composition database (CIIQUAL 95). Nutritional data were obtained from the producer of commercial products and added to the database. Calcium source was also reported. Dairy products were specified (natural yoghourt, sweetened yoghourt, soft white cheese) and average contribution of cheese was noted. Average contribution of fruits and vegetables and calcium from water were also reported. In case of tap-water consumption, average concentration of calcium was considered at 81 mg/l according to the data of the CAP (Community d’Agglomeration de Poitiers).

Energy, lipid, carbohydrates, protein and calcium intake were reported. The distinction between dairy and mineral calcium was considered.

Biological determinations

Fasting glucose was measured using the glucose oxidase method (PAP glucose, Biomerieux kit, Lyon, France). HPLC was used to measure the HbA1c concentration on blood samples collected on EDTA (Menarini, Rungis, France). Normal values range from 4 to 6%.

Total cholesterol, HDL-cholesterol and triglycerides were measured in the fasting state (Roche Diagnostics; Meylan, France). LDL-cholesterol was calculated using the...
Friedewald formula if the triglyceride level was lower than 4.75 mmol/l [19]. Serum calcium was determined using a colorimetric method (Roche Diagnostics; Meylan, France).

**Statistical analysis**

Data are given as mean ± one SD or as median (interquartile ranges). Categorical variables were analysed with the chi-square test or with the Fisher’s exact test. Continuous variables were examined with ANOVA or with Kruskall-Wallis tests if data were not normally distributed. Comparison between baseline and final data was performed using the paired t-test or with Wilcoxon’s test. Correlation between continuous variables was examined using the non parametric Spearman test. Comparisons regarding waist circumference or waist to hip ratio were adjusted for sex.

A two-sided P value of <0.05 was considered to be statistically significant.

**Results**

Thirty-one patients, 18 males and 13 females, aged 62 ± 9 years were studied. Duration of follow-up was 5.5 ± 0.6 months.

Mean duration of diabetes was 14 ± 10 years. At the final visit, insulin dose was 0.42 ± 0.32 UI/kg/day. Half of our patients were treated with insulin associated with metformin. The majority of study participants had hypertension (74%) and 35% of hypertensive subjects were treated by diuretics.

Calcium intake did not change between the two visits even if energy intake decreased due to a decreased carbohydrate consumption at final visit (table I).

Clinical and biological characteristics are summarized in table II. Patients mean weight gain was 2.4 kg (IQR= -1.15 to +5.27 kg). Waist circumference increased by 2 cm (IQR= 0 to +4 cm). Glycaemic control was significantly better at the final visit with a median difference of HbA1c of -2.5% (IQR= -3.6 to –0.8%).

Clinical and biological characteristics according to tertile of mean calcium intake at initial and final visit are summarized in table III. Baseline BMI was not significantly different according to calcium intake (P=0.0866): 29.5±4.6 (first tertile), 33.6±7.8 (second tertile), 28.4±2.4 (third tertile). There was no difference in weight change or waist circumference change, according to calcium intake. Adjustment on baseline body weight or BMI did not modify the results.

We did not find any correlation between weight change and total calcium intake (Rho=0.186; P=0.3165) or dairy calcium intake (Rho=0.191; P=0.3040). Similarly, we did not find any correlation between waist circumference change and total calcium intake (Rho=0.285; P=0.1205) or dairy calcium intake (Rho=0.324; P=0.0755).

Considering calcium intake at initial and final visit rather than the mean of the two visits did not modify the results (unshown data).

**Discussion**

In this observational study, we analysed weight change secondary to initiation of insulin therapy, according to daily calcium intake, for the first time in type 2 diabetic patients. We failed to find any association between daily total or dairy calcium intake and weight change or waist circumference change in newly insulin treated type 2 diabetic patients. We did not find any association between calcium intake and BMI or waist circumference at baseline or at follow-up, at variance with epidemiological and observational studies [4,20,21].

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Final</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy (Kcal/day)</td>
<td>1660±592</td>
<td>1547±500</td>
</tr>
<tr>
<td>Energy/kg of bodyweight</td>
<td>20.6±7.3</td>
<td>18.6±5.8</td>
</tr>
<tr>
<td>Carbohydrate (g/d)</td>
<td>188±83</td>
<td>164±51</td>
</tr>
<tr>
<td>Fat (g/d)</td>
<td>67±29</td>
<td>62±24</td>
</tr>
<tr>
<td>Protein (g/d)</td>
<td>71±25</td>
<td>70±21</td>
</tr>
<tr>
<td>Total calcium (mg/d)</td>
<td>839.7±321.3</td>
<td>749.2±239.1</td>
</tr>
<tr>
<td>Total calcium/Energy (mg/kcal)</td>
<td>0.55±0.24</td>
<td>0.51±0.19</td>
</tr>
<tr>
<td>Dairy calcium (mg/d)</td>
<td>388.4±250.9</td>
<td>351.3±230.5</td>
</tr>
<tr>
<td>Dairy calcium/Energy (mg/kcal)</td>
<td>0.26±0.17</td>
<td>0.24±0.16</td>
</tr>
<tr>
<td>Water calcium (mg/d)*</td>
<td>135 (45-180)</td>
<td>104 (46-150)</td>
</tr>
<tr>
<td>Water calcium/Energy (mg/kcal)*</td>
<td>0.085 (0.027-0.113)</td>
<td>0.084 (0.029-0.113)</td>
</tr>
</tbody>
</table>

P=comparison was performed using the paired t-test or Wilcoxon’s test, Data are mean ± SD or median (IQR) when specified*.
In our study, calcium intake was concordant with the consumption observed in the French population; in a majority of subjects, calcium intake was below advised nutritional contribution [22]. Mean weight gain shortly after initiation of insulin therapy in our study was 2.9 kg, which is concordant with the results of UKPDS [13] and other studies [23-25].

The composition of weight gain during insulin treatment is not well understood. Insulin exerts an anabolic effect on both lipid and protein metabolism, and promotes water and salt retention [15]. Recently, Salle et al showed that weight gain secondary to insulin therapy was composed by 50% of fat and by 33% of fat-free mass [15], which was confirmed by Packiananthan et al [16]. Calcium intake could counteract the effect of insulin on the increase of the fat mass, even if our present data are negative. We did not find any association between weight change and total daily calcium intake.

### Table II
Clinical characteristics at baseline and final visits.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Final</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (Kg)</td>
<td>81.9±16.2</td>
<td>84.8±17.8</td>
<td>0.0272</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>30.4±5.6</td>
<td>31.5±11.7</td>
<td>0.0193</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>107±13</td>
<td>110±12</td>
<td>0.0161</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>134±15</td>
<td>137±14</td>
<td>0.2182</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>71±9</td>
<td>78±7</td>
<td>0.2283</td>
</tr>
<tr>
<td>FPG (mmol/l)</td>
<td>10.86±4.00</td>
<td>7.67±2.57</td>
<td>0.0008</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>9.5±1.9</td>
<td>7.1±0.8</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**Table III**
Clinical and biological characteristics at the end of the study according to tertile of calcium intake.

<table>
<thead>
<tr>
<th></th>
<th>total population</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium intake (mg/d)</td>
<td>568±144</td>
<td>778±28</td>
<td>1060±243</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>18/13</td>
<td>6/5</td>
<td>6/4</td>
<td>6/4</td>
<td>0.2275</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>84.8±17</td>
<td>77.3±8.8</td>
<td>96.3±24.5</td>
<td>81.6±12.0</td>
<td>0.0351</td>
</tr>
<tr>
<td>Weight change (Kg)*</td>
<td>2.40 (-1.15-5.27)</td>
<td>1.90 (-0.90-3.75)</td>
<td>3.45 (-1.00-6.90)</td>
<td>2.65 (-1.20-10.00)</td>
<td>0.5744</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>31.5±5.7</td>
<td>29.2±3.9</td>
<td>35.2±7.4</td>
<td>30.3±3.6</td>
<td>0.0335</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>110±12</td>
<td>105±8</td>
<td>117±14</td>
<td>108±11</td>
<td>0.0399</td>
</tr>
<tr>
<td>Waist circumference change (cm)*</td>
<td>2 (0-4)</td>
<td>0.5 (0.0-4.5)</td>
<td>1 (0.0-2.0)</td>
<td>3 (0.0-6.0)</td>
<td>0.6106</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>137±14</td>
<td>137±15</td>
<td>140±17</td>
<td>134±10</td>
<td>0.6944</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>78±7</td>
<td>78±6</td>
<td>78±8</td>
<td>77±8</td>
<td>0.8653</td>
</tr>
<tr>
<td>Serum calcium (mmol/l)</td>
<td>2.29±0.11</td>
<td>2.25±0.08</td>
<td>2.28±0.14</td>
<td>2.36±0.11</td>
<td>0.1577</td>
</tr>
<tr>
<td>FPG (mmol/l)</td>
<td>7.7±2.6</td>
<td>6.9±1.6</td>
<td>7.6±2.0</td>
<td>8.4±3.6</td>
<td>0.4920</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.1±0.8</td>
<td>6.9±0.9</td>
<td>7.2±0.7</td>
<td>7.2±0.9</td>
<td>0.5704</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)*</td>
<td>1.54 (1.25-2.23)</td>
<td>1.41 (0.84-1.93)</td>
<td>1.74 (1.23-2.37)</td>
<td>2.09 (1.42-2.16)</td>
<td>0.3067</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>5.11±1.05</td>
<td>4.91±1.15</td>
<td>5.28±1.00</td>
<td>5.09±1.12</td>
<td>0.7755</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/l)</td>
<td>1.25±0.35</td>
<td>1.42±0.53</td>
<td>1.24±0.28</td>
<td>1.10±0.12</td>
<td>0.1785</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/l)</td>
<td>2.96±0.59</td>
<td>2.86±0.66</td>
<td>3.19±0.66</td>
<td>2.77±0.35</td>
<td>0.2955</td>
</tr>
</tbody>
</table>

Calcium intake: mean estimation of daily calcium intake, according to 7-day diet history at initial and final visits. BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FPG: Fasting plasma glucose. Data are mean ± SD or median (Interquartile range) when specified.*
calcium intake or dairy calcium intake. Recently, dairy consumption was found to be inversely correlated with the incidence of insulin resistance [21] and to be protective for the development of type 2 diabetes independently of age, family history of diabetes, and body mass index [26]. Rosell et al have reported an inverse relationship between daily calcium intake and abdominal obesity [27].

There are few randomised controlled studies which analysed the effect of calcium intake on weight change. In the meta-analysis of Davies et al, [7], the authors reported a significant negative association between daily calcium intake and body-weight in 780 women. Other studies reported a positive effect specific of dairy calcium on weight loss [8,10,11]. Two studies however, reported no association between calcium supplementation and weight loss in premenopausal and menopausal women [28,29]. In these studies, calcium was supplemented as citrate and not as dairy form.

The mechanism underlying the effect of calcium on weight change is based on intracellular calcium levels. Dietary calcium suppresses 1,25 dihydrovitamin D3 induced calcium influx, stimulates lipolysis, inhibits de novo lipogenesis via inhibiting FAS expression and activity, and increases white adipose tissue UCP2 expression and core temperature [5,17,30,31].

Consistent with this, Melanson et al [32] have shown that acute calcium intake is significantly related to fat oxidation measured using whole-room, indirect calorimetry. Milk is a rich source of bioactive compounds [33] that may act independently or synergistically with the suppression of 1,25 dihydrovitamin D3 to favourably affect fat loss [11]. Peptides as caseinomacropeptide and casomorphine issued from digestion of casein could be efficient on food catch via the modulation of gastrointestinal hormones [34]. This could explain the greater anti-obesity effect of dairy source of calcium.

It is important to mention some limitations of our study. We did an observational study with a small number of patients corresponding to a pilot study to analyse the effect of calcium intake, assessed using a 7-day food history, on weight change in diabetic subjects. However, these preliminary results do not support a major influence of calcium on weight in diabetic subjects. In addition, the baseline metabolic control was poor in our patients and considerably improved with insulin. This could hide any potential effect on calcium intake, leading to a falsely negative result, given the small number of patients The BMI at baseline was approximately 30 in our population, which could influence weight gain; however the lack of effect of calcium intake on weight gain was not modified after adjustment on baseline BMI.

In conclusion, we found that calcium intake was not associated with weight change in the first six months following initiation of insulin in type 2 diabetes patients. However, an interventional trial could be helpful to confirm the preliminary negative results of this observational pilot study.

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References