Calcium consumption and insulin resistance syndrome parameters. Data from the Epidemiological Study on the Insulin Resistance Syndrome (DESIR).

Peggy Drouillet, Beverley Balkau, Marie-Aline Charles, Sylviane Vol, Martine Bedouet, Pierre Ducimetière, The Desir Study Group

Nutrition, metabolism, and cardiovascular diseases : NMCD 17, 7 (2007) 486-92

Calcium consumption and insulin resistance syndrome parameters. The D.E.S.I.R. study (Data from an Epidemiological Study on the Insulin Resistance syndrome).

Peggy Drouillet[a,b,*], Beverley Balkau[a,b], Marie Aline Charles[a,b], Sylviane Vol[c], Martine Bedouet[c], Pierre Ducimetière[a,b], The D.E.S.I.R. Study Group[c]

[a] *INSERM U780-IFR69, Villejuif, France.*

[b] *Univ Paris-Sud, Faculté de Médecine, Villejuif, France*

[c] *IRSA, La Riche, France.*

Running title: Calcium consumption and insulin resistance syndrome parameters

*Correspondance :

Peggy Drouillet

INSERM U780. 16 Avenue Paul Vaillant Couturier

94807 Villejuif cedex. France

Telephone : 33 1 45 59 50 71 / FAX : 33 1 47 26 94 54

e-mail : drouillet@vjf.inserm.fr

ABSTRACT

Background and aims: A number of studies have investigated the role of dietary calcium in lipid metabolism and weight regulation and the role of dairy products on the incidence of the insulin resistance syndrome. We study the relation between dietary calcium and insulin resistance syndrome parameters.

Methods and results: The studied population (n=4372) were included in the D.E.S.I.R. cohort. Data on the syndrome elements: glucose, serum insulin, triglycerides, HDL-cholesterol concentrations, waist circumference and blood pressure were measured. Total energy, calcium and alcohol intake were estimated using a food frequency questionnaire. Relations between dietary calcium density and the syndrome elements were analysed by multiple linear regression models, adjusted on age, smoking, alcohol consumption and physical activity.

From one quartile of calcium density to the following quartile, the means of systolic and diastolic blood pressures and insulin concentration decreased in women by 0.9 mmHg, 0.5 mmHg and 2.4% and HDL cholesterol increased by 0.007 mmol/l (all $p<0.05$) respectively after adjustment for age, smoking, alcohol intake and physical activity. In men, there was an increase in BMI of 0.2 kg/m^2 and a decrease in diastolic blood pressure of 0.4 mmHg (both $p < 0.05$).

Conclusion: These results confirm, in women only, a beneficial association between dietary calcium and arterial blood pressure as well as with insulin and HDL-cholesterol concentrations, whereas in men there was only a beneficial association with diastolic blood pressure.

Key-words: Calcium Consumption, Diet, Insulin Resistance Syndrome, Epidemiology, Metabolic Syndrome

INTRODUCTION

According to the description by Reaven, the insulin resistance syndrome is associated with cardiovascular disease and diabetes [1]. This syndrome involves insulin resistance, hyperinsulinemia, hyperglycemia, central adiposity, arterial hypertension, hypertriglyceridemia, and hypo-HDL-cholesterolemia.

Dietary calcium is known for its role in the prevention of osteoporosis, hypertension, some cancers [2], and recently a number of studies show its role in lipid metabolism and in weight regulation. Zemel et al. find in both sexes, an inverse relation between dietary calcium and fat mass, after adjustment on total energy intake, physical activity, age and ethnic origin [3]. From a meta-analysis of five clinical studies in women, Davies et al. show an inverse relation between body mass index (BMI) and dietary calcium [4]. Other studies find inverse relations between calcium consumption and adiposity and cardiovascular diseases [5]. A recent article from the CARDIA Study (Coronary Artery Risk Development in Young Adults Study) shows that the incidences of obesity, abnormal glucose homeostasis, hypertension, are inversely proportional to the consumption of dairy products for overweight but not for normal weight subjects [6]. However, in a cross-sectional study in a native American population, Narayan et al. find a positive association between dietary calcium and blood pressure [7]. Bowen et al. report no effect of dietary calcium or protein sources on weight loss, and Thompson et al. in a randomised trial, shows similar results [8-9]. Lastly, Ma et al. find that calcium intake, but not dairy intake, is associated with insulin sensitivity [10]. Thus, the impact of dietary calcium on the insulin resistance syndrome parameters is a subject of debate.

The aim of this study was to evaluate the association between calcium consumption and the insulin resistance syndrome parameters in a French population.

METHODS

Study cohort

The subjects are men and women aged 30 to 65 years, who participated in the D.E.S.I.R. (Data from an Epidemiological Study on the Insulin Resistance syndrome) Study, a 9-year follow-up study that aims to clarify the development of the insulin resistance syndrome. Subjects were volunteers who came from 10 Health Examination Centres in the western central part of France. In total, 5 212 individuals participated in the D.E.S.I.R. study [11]. For the analyses, 103 subjects were not included because they were diabetic. As we were interested in calcium consumption, the 448 subjects who declared to be on a diet, 210 who did not answer all the questions in the food frequency questionnaire and the 79 subjects who took medications which could be a source of calcium were excluded. The population studied included thus 2 235 men and 2 137 women. The study was approved by the ethics committee of the Kremlin Bicêtre Hospital, and all participants signed an informed consent.

Measures

Clinical measurements were carried out as routinely in the setting of a clinical check-up and thus were measured only once, by one or two operators in each of the ten centres, according to a written, standardised protocol. Height was measured with a stadiometer and weight on barefooted, lightly clad subjects and the body mass index (BMI: weight/height^2) was calculated. Waist circumference (the smallest circumference between lower ribs and iliac crests) was measured by a doctor using a tape measure. The doctor also assessed twice, systolic and diastolic blood pressures at rest, after at least five minutes, in a supine position, on the right arm using a mercury sphygmomanometer, and the second of the two measures were used. For biological measures, blood samples were collected in the morning after 12 hours of fast. Insulin was assayed on serum by a specific enzyme immunoassay (MEIA) with

an Abbott IMX; fasting plasma glucose was determined by the glucose-oxidase method using a Technicon RA 1000 or a KONE; HDL-cholesterol and triglycerides were assayed on plasma by the enzymatic Trinder method using a Technicon DAX24 or with a KONE. Data on pharmacological treatment, particularly for blood pressure and lipid lowering drugs were recorded.

Smoking habits and physical activity were assessed using self-administrated questionnaires. Subjects were asked their daily cigarette consumption and to note their physical activity levels at home, at work (for both items: low, moderate, high, intense) and sport during their leisure time (low (never), moderate (less than once per week), high (one to two times per week), intense (more than twice per week). Physical activity was then recoded into three classes: **high** if at least one of the physical activities was intense or if sport was high and at least one other activity was high; **moderate** if at least one of the activities was high or if activity both at home and at work were moderate; **low** otherwise.

An 18 item food frequency questionnaire (the NAQA questionnaire) was completed by each participant. Questions asked about the frequencies and the levels of consumption of different foods [12]. Calcium, alcohol and total energy intake have been estimated from the NAQA questionnaire, using regression equations determined from a validation study [12]. Total energy intake (without alcohol) was estimated from the questions on the type of breakfast, meat, fish, eggs, pork products, fried food, butter, cheese, other dairy products (milk, yoghurt, cream cheese, etc), bread and sugar products (desserts, sweets). Alcohol intake was determined from questions on the intake of wine, beer/cider and spirits. The estimation of dietary calcium used the questions on the consumption of fish, butter, cheese and dairy products.

Statistical methods

All analyses were performed with the Statistical Analysis System, version 9. Due to the skewness of their distributions, insulin and triglycerides concentrations were log-transformed. A χ^2 test was used to compare characteristics of subjects included and excluded from the analyses. The relation between insulin resistance syndrome parameters (waist circumference, systolic and diastolic blood pressures, triglycerides, HDL-cholesterol, insulin and glucose concentrations) and dietary calcium density (calcium consumption / energy intake (without alcohol)) were analysed by multiple linear regression models, after adjustments for potential confounders. Dietary calcium density was studied in sex-specific quartiles, and the results are presented as the increase in the insulin resistance syndrome parameters for an increase in calcium density from one quartile group to the next. The linearity of the relations between calcium density quartile and insulin resistance syndrome parameters was confirmed. The p value corresponds to a linear trend test over the four calcium density classes; the criterion for statistical significance was p=0.05. As potential confounders, we included age, alcohol consumption (continuous covariate), smoking (yes/no) and physical activity (three classes used as a continuous covariate), BMI, as well as lipid intake (from the questions on the consumption of meat, fish, pork products, fried foods, butter, cheese and other dairy products). Men and women were analysed separately.

RESULTS

Characteristics of participants

Differences in dietary intake were observed between participants who were included and excluded from our study, and were due to the reasons for exclusion (diabetes, on a diet), which can change dietary intake. Those excluded reported significantly lower intake of butter, sugared products and cheese and more fish. Excluded women consumed more dairy products ($p<0.01$), whereas the opposite was observed for men ($p<0.05$). Moreover, excluded men drank more wine and beer but less spirits than men who were included. For the 4 372 subjects included in our study, there were differences in consumption between men and women. Men ate more meat but less fish, more 'fatty' food (butter, fried food) and sugared products than women. Moreover men ate more cheese, whereas women ate more of other dairy products.

Characteristics of the population studied are presented in Table 1. Men had a total energy intake of 2 543 kcal/day (from 1 500 to 4 000 kcal/day), whereas women had an intake of 1 754 kcal/day (from 1 200 to 2 600 kcal/day), and intake decreased with age in men, and women until 60 years. Dietary calcium ranged between 688 and 1 826 mg/day, with an average consumption of 1 109 mg/day for men and 980 mg/day for women. Calcium consumption decreased with age ($p<0.0001$). Nevertheless, dietary calcium density did not change significantly with age (Fig.1) but decreased with alcohol consumption ($p<0.0001$).

Association between calcium consumption and insulin resistance syndrome parameters

Dietary calcium density was significantly related to some of the insulin resistance syndrome parameters, particularly in women (Table 2). In women after adjustment on age, the mean insulin concentration decreased as calcium increased, by 2.3% from one quartile of dietary calcium density to the next ($p=0.02$). The same trend was observed for triglycerides, with a

decrease of 1.8% from one quartile to the next one (p=0.06), HDL-cholesterol concentration increased by 0.006 mmol/l (p=0.04); systolic blood pressure decreased by 0.959 mmHg (p=0.001) and diastolic blood pressure decreased by 0.493 mmHg (p=0.004) (Fig.2). For men, the only significant relations observed were for diastolic blood pressure which decreased by 0.448 mmHg from one quartile to the next (p=0.01), while there was an increase in BMI of 0.132 kg/m² (p=0.03).

Adjustments were made on behavioural factors that could be confounders in the relation between calcium intake and the syndrome parameters: alcohol consumption, smoking and physical activity. The results changed little (Table 2). In women, from one quartile to the next, the mean insulin concentration decreased by 2.4% (p=0.01), HDL-cholesterol concentration increased by 0.007 mmol/l (p=0.02), systolic blood pressure decreased by 0.872 mmHg (p=0.002) while diastolic blood pressure decreased by 0.456 mmHg (p=0.01). In men, the diastolic blood pressure decreased significantly by 0.358 mmHg between successive quartiles (p=0.05), and there was an increase in BMI of 0.169 kg/m² between calcium density quartiles (p=0.01).

When further adjustments on BMI and lipid intake were made, an increase in calcium intake became beneficially associated with central adiposity: with increasing calcium density, the mean waist circumference was 0.202 cm lower in men (p=0.02) and 0.190 cm lower in women (p=0.05). In women the relation between calcium intake and HDL-cholesterol was no longer significant, but the relations with insulin and blood pressure became stronger. In men the relation between calcium intake and diastolic blood pressure remained.

After exclusion of participants who took pharmacological treatment for blood pressure or lipid lowering drugs (n=650), the results did not change.

DISCUSSION

The results of our study confirm the association of dietary calcium with lower blood pressure in those who consumed more calcium. As Zemel [13-14], we found a relationship with diastolic blood pressure in both sexes, but only in women for systolic blood pressure. In women, we also found a positive relation between calcium consumption and insulin concentration in agreement with the study of Zemel cited above [14] and with a study in women from the UK who were classed according to milk-drinking habits [15]. Moreover calcium consumption seemed to be associated with a better HDL-cholesterol concentration in women, with no effect on triglycerides. After adjustments for BMI and lipid intake, calcium consumption was no longer associated with HDL-concentration, which means that this association is at least partly dependent on lipid intake and BMI. That the results are only significant for women could be explained by the higher dietary calcium density in women than in men. In men, we observed an increase in BMI between calcium density quartiles which is not consistent with the calcium-adiposity literature [3-5, 14, 17]. Nevertheless, increasing dairy product consumption has been reported to increase lean mass [18], and this could explain the observed increase in BMI. After adjustments for BMI, the observed decrease in central adiposity, in men and women, with increasing calcium density is consistent with the literature.

A positive feature of this study is the number of subjects studied. Moreover, exclusion of subjects who were diabetic or on a diet eliminated those whose health might have meant they have modified their diet and hence some of their biological parameters. Exclusion of people

who did not answer all the questions of the food frequency questionnaire prevented an under-estimate of consumption.

The dietary questionnaire is a limitation in our study as it is quite short, eighteen questions. However, it is suitable for determining alimentary habits in clinical practice in preventive medicine centres and is suitably short to be well answered in an epidemiological study [12]. As with all food-frequency questions, the accuracy of the responses (under- or over-consumption) is difficult to evaluate. We may have over-evaluated the consumption of calcium with a semi-quantitative questionnaire but the range of our values are not so far from the range of intake observed in the 1998-1999 cross-sectional French INCA (Enquête Individuelle et Nationale sur les Consommations Alimentaires) food consumption survey: mean calcium consumption of 910 ± 331 mg/day for men and 819 ± 272 mg/day for women. Their estimation should be more precise than ours because of the more detailed questionnaire they used [16].

Another limitation of this study is that the clinical parameters were measured only once, and their lower precision may mean that relations are more difficult to show.

Our study deals with the relation between insulin resistance syndrome parameters and dietary calcium, and not with consumption of dairy products. Many studies have shown the impact of dairy products on various parameters of the insulin resistance syndrome [6, 13-15, 17-20]. Recently, dairy products have been shown to be protective for the incidence of diabetes [21]. The association of dietary calcium with lower blood pressure is now well-documented [22-25]. There is only one other publication, in US women, which evaluates the impact of dietary calcium on syndrome parameters and the syndrome itself, from more than 10,000 participants

in the Women's Health Study [26]. Increasing dietary calcium was significantly related with lower abdominal adiposity, lower BMI, hypertriglyceridemia, arterial blood pressure, lower incident diabetes – and a lower frequency of the insulin resistance syndrome. This large study with a comprehensive food frequency questionnaire has better power to detect associations. Finally, Ma et al also found a relationship between calcium intake and insulin sensitivity, but not with dairy intake [10].

In conclusion, a prospective study in our cohort is now required to show the long term effect of dietary calcium on the insulin resistance syndrome parameters, after 9 years of follow-up.

ACKNOWLEDGEMENTS

The D.E.S.I.R. Study Group: INSERM U258: B Balkau, P Ducimetière, E Eschwège; INSERM U367: F Alhenc-Gelas; CHU D'ANGERS: Y Gallois, A Girault; Hôpital Bichat: F Fumeron, M Marre; CENTRES D'EXAMENS DE SANTÉ du RÉSEAU 9: Alençon - INSTITUT DE RECHERCHE EN MÉDECINE GÉNÉRALE: J Cogneau; MEDECINS GÉNERALISTES des Départements; INSTITUT INTER RÉGIONAL POUR LA SANTÉ: C Born, E Cacès, M Cailleau, JG Moreau, F Rakotozafy, J Tichet, S Vol.

This study was supported by INSERM, CNAMTS, the Association Diabète Risque Vasculaire, the Fédération Française de Cardiologie, La Fondation de France, ALFEDIAM, ONIVINS, Ardix Medical, Bayer Diagnostics, Becton Dickinson, Cardionics, Lipha Pharmaceuticals, Lilly, Merck Santé, Novartis Pharma, Novo Nordisk, Pierre Fabre, Roche, Sanofi-Aventis, Topcon.

REFERENCES

[1] Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. Diabetes 1988;37:1595-1607.

[2] Huth PJ, DiRienzo DB, Miller GD. Major scientific advances with dairy foods in nutrition and health. J Dairy Sci 2006;89:1207-1221.

[3] Zemel MB, Shi H, Greer B, Dirienzo D, Zemel PC. Regulation of adiposity by dietary calcium. Faseb J 2000;14:1132-8.

[4] Davies KM, Heaney RP, Recker RR, Lappe JM, Barger-Lux MJ, Rafferty K, et al. Calcium intake and body weight. J Clin Endocrinol Metab 2000;85:4635-8.

[5] Jacqmain M, Doucet E, Despres JP, Bouchard C, Tremblay A. Calcium intake, body composition, and lipoprotein-lipid concentrations in adults. Am J Clin Nutr 2003;77:1448-52.

[6] Pereira MA, Jacobs DR, Jr., Van Horn L, Slattery ML, Kartashov AI, Ludwig DS. Dairy consumption, obesity, and the insulin resistance syndrome in young adults: the CARDIA Study. Jama 2002;287:2081-9.

[7] Narayan KM, Hanson RL, Smith CJ, Nelson RG, Gyenizse SB, Pettitt DJ, et al. Dietary calcium and blood pressure in a Native American population. J Am Coll Nutr 1998;17:59-64.

[8] Bowen J, Noakes M, Clifton PM. Effect of calcium and dairy foods in high protein, energy-restricted diets on weight loss and metabolic parameters in overweight adults. Int J Obes (Lond) 2005;29:957-965.

[9] Thompson WG, Rostad Holdman N, Janzow DJ, Slezak JM, Morris KL, Zemel MB. Effect of energy-reduced diets high in dairy products and fiber on weight loss in obese adults. Obes Res 2005;13:1344-1353.

[10] Ma B, Lawson AB, Liese AD, Bell RA, Mayer-Davis EJ. Dairy, magnesium, and calcium intake in relation to insulin sensitivity: approaches to modeling a dose-dependent association. Am J Epidemiol 2006;164:449-458.

[11] Balkau B, Vernay M, Mhamdi L, Novak M, Arondel D, Vol S, et al. The incidence and persistence of the NCEP (National Cholesterol Education Program) metabolic syndrome. The French D.E.S.I.R. study. Diabetes Metab 2003;29:526-32.

[12] Lasfargues G, Vol S, Le Clesiau H, Bedouet M, Hagel L, Constans T, et al. [Validity of a short self-administered dietary questionnaire compared with a dietetic interview]. Presse Med 1990;19:953-7.

[13] Zemel MB, Richards J, Milstead A, Campbell P. Effects of calcium and dairy on body composition and weight loss in African-American adults. Obes Res 2005;13:1218-1225.

[14] Zemel MB, Richards J, Mathis S, Milstead A, Gebhardt L, Silva E. Dairy augmentation of total and central fat loss in obese subjects. Int J Obes (Lond) 2005;29:391-7.

[15] Lawlor DA, Ebrahim S, Timpson N, Davey Smith G. Avoiding milk is associated with a reduced risk of insulin resistance and the metabolic syndrome: findings from the British Women's Heart and Health Study. Diabet Med 2005;22:808-11.

[16] Volatier JL. Enquête INCA individuelle et nationale sur les consommations alimentaires. Ed TEC & DOC, Paris, Lavoisier, 2000.

[17] Parikh SJ, Yanovski JA. Calcium intake and adiposity. Am J Clin Nutr 2003;77:281-7.

[18] Zemel M. Calcium modulation of adiposity. Obes Res 2003;11:375-376.

[19] Zemel MB. Regulation of adiposity and obesity risk by dietary calcium: mechanisms and implications. J Am Coll Nutr 2002;21:146S-51S.

[20] Azadbakht L, Mirmiran P, Esmaillzadeh A, Azizi F. Dairy consumption is inversely associated with the prevalence of the metabolic syndrome in Tehranian adults. Am J Clin Nutr 2005;82:523-30.

[21] Choi HK, Willett WC, Stampfer MJ, Rimm E, Hu FB. Dairy consumption and risk of type 2 diabetes mellitus in men: a prospective study. Arch Intern Med 2005;165:997-1003.

[22] Schroder H, Schmelz E, Marrugat J. Relationship between diet and blood pressure in a representative Mediterranean population. Eur J Nutr 2002;41:161-7.

[23] Resnick LM. The role of dietary calcium in hypertension: a hierarchical overview. Am J Hypertens 1999;12:99-112.

[24] McCarron DA, Metz JA, Hatton DC. Mineral intake and blood pressure in African Americans. Am J Clin Nutr 1998;68:517-8.

[25] Dwyer JH, Dwyer KM, Scribner RA, Sun P, Li L, Nicholson LM, et al. Dietary calcium, calcium supplementation, and blood pressure in African American adolescents. Am J Clin Nutr 1998;68:648-55.

[26] Liu S, Song Y, Ford ES, Manson JE, Buring JE, Ridker PM. Dietary calcium, vitamin D, and the prevalence of metabolic syndrome in middle-aged and older U.S. women. Diabetes Care 2005;28:2926-32.