ORIGINAL RESEARCH

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Plasma vitamin D levels and risk of metabolic syndrome in Canadians

Abstract

Purpose: Vitamin D deficiency has been implicated in susceptibility to the development of metabolic syndrome, obesity and type 2 diabetes mellitus. The present study aimed to quantify the association between vitamin D plasma level, the number of metabolic syndrome components and insulin resistance in Canadians.

Methods: Vitamin D plasma level and clinical data were determined from 1,818 subjects from the Canadian Health Measures Survey; a representative health survey of the general population of Canada conducted from 2007 to 2009. The definition of metabolic syndrome was based on the National Cholesterol Education Program, Adult Treatment Panel III criteria. Adjusted general linear models were used to estimate the association between vitamin D level and probability of having metabolic syndrome, as well as the association between plasma vitamin D and insulin resistance (homeostasis model assessment for insulin resistance, or HOMA-IR).

Results: The prevalence of metabolic syndrome in the study population was 8.9%. The number of metabolic syndrome components was inversely correlated with plasma vitamin D level ($\rho = -0.1$, $p < 0.0001$). Subjects in the highest vitamin D quartile had lower odds ratio of metabolic syndrome compared with their counterparts in the lowest vitamin D quartile (0.50, 95% CI= 0.24-1.06). Increasing plasma vitamin D level (by 10 nmol/L) was inversely associated with HOMA-IR score ($\beta = -0.08$, $p = 0.006$) in a model adjusted for physical activity, smoking status, month of interview, age, sex and ethnicity.

Conclusion: Vitamin D plasma levels are associated with the occurrence of metabolic syndrome components and insulin resistance among Canadians and are linked to increased level of insulin resistance.

Manuscript submitted 29th June, 2011

Manuscript accepted 16th September, 2011

Clin Invest Med 2011; 34 (6): E377-E384.

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Metabolic syndrome is strongly predictive of type 2 diabetes mellitus (T2DM) and cardiovascular diseases [1]. The estimated prevalence of metabolic syndrome in Canada is 14% [2], and its prevalence is increasing globally [3]. The consensus of available information implicates low serum vitamin D levels as a factor that influences the development of a range of pre-diabetic conditions such as metabolic syndrome and insulin resistance [4,5]. These findings are supported by observations from populations around the world, including the US [6], Europe [7], New Zealand [8] and Asia [9], and are thought to be related to the immunomodulatory function of vitamin D. Recently, it was proposed that vitamin D plays a role in attenuating innate immunity-related low-grade chronic inflammation, which is a predisposing factor for the onset of metabolic syndrome and the subsequent manifestation of T2DM and cardiovascular diseases [10].

Despite the overall inverse association observed between vitamin D intake or serum level, and the development of metabolic syndrome, findings are still conflicting; for example, serum vitamin D concentration was not correlated with insulin action or secretion in Europeans with metabolic syndrome [11]. Therefore, additional investigations are warranted to further explore this association in different populations. Given the role of metabolic syndrome in the later manifestation of T2DM and cardiovascular diseases, if a causal relationship between vitamin D and these chronic disorders can be substantiated, strategies to improve vitamin D status may be proposed in a public health setting, given the recent evidence demonstrating vitamin D insufficiency in the Canadian population [12].

The present study was undertaken in an attempt to quantify the association among plasma vitamin D levels, the extent of metabolic syndrome and insulin resistance in a representative sample of the general Canadian population using data from the Canadian Health Measures Survey (CHMS) [13].

Methods

The Study Population

Data from the Canadian Health Measures Survey (CHMS) (cycle 3.1) were used in the present study to examine the association between vitamin D serum levels and risk of metabolic syndrome [13]. The Canadian Health Measures Survey (CHMS) is a population-based survey designed to collect health and wellness indicators in Canadians aged 6-79 years. The survey was conducted between 2007 and 2009, using a multi-stage sampling strategy and is representative of 96.3% of the Canadians when weighting schemes are applied. Residents of Indian reserves, Crown lands, certain remote regions, insti-

tutions and full-time members of the Canadian Forces were excluded from the survey. The CHMS selected 8,772 dwellings and 6,106 agreed to participate (household response rate: 69.6%). From these households, 7,483 people were included in the survey and 6,604 agreed to participate in the study questionnaire (response rate: 88.3%). Of the latter, 5,604 agreed to undergo physical measurements (response rate: 84.9%). From the 5,604 subjects available, persons under the age of 16 years, non-fasting responders, subjects who had fasting plasma glucose (FPG) levels >7.0 mmol/L as they may have, or are at risk of, T2DM, and patients who reported to ever being diagnosed with diabetes by a health professional were excluded from this study. The final unweighted number of subjects in the present analysis was 1,818 individuals (weighted number = 24,120,330 Canadians). Nationally, the response rate was 51.7%. Detailed information about the CHMS survey methodology has been described elsewhere [13].

The Metabolic Syndrome Components and Analyses

The US National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) definition of metabolic syndrome [14] was used in this study population rather than other classification systems, such as the criteria set by the International Diabetes Federation or the WHO, as the complete data required for metabolic syndrome classification were only available for the NCEP ATP III definition. Under these classification criteria, an individual was classified as having metabolic syndrome if (s)he had three or more of the following components: waist circumference (WC) >102 cm (male) or >88 cm (female), triglycerides (TG) ≥ 1.7 mmol/L, high density lipoprotein-cholesterol (HDL-C) <40mg/dL (1.03 mmol/L) in males or <50 mg/dL (1.29 mmol/L) in females, blood pressure (BP) $\geq 130/85$ mmHg, and fasting plasma glucose (FPG) ≥ 6.1 mmol/L (110 mg/dL).

All laboratory assays were conducted by Health Canada laboratories. Details of the standard laboratory procedures used are available online [15]. Plasma 25(OH)D levels among subjects in the CHMS were measured in nmol/L by a chemiluminescence assay using the LIAISON 25-hydroxyvitamin D TOTAL assay (Diasorin, Ltd., Stillwater, MN, USA). Preliminary testing of this assay using external quality controls from BioRad and Diasorin estimated coefficients of variation (CVs) within runs as ranging between 3.2 and 8.5%, and between runs CVs as between 6.9-12.7%. Health Canada samples were within these limits. For more detailed information on the collection and measurement of plasma 25(OH)D in the CHMS, refer to the *Vitamin D Reference Laboratory Standard Operating Procedures Manual* at www.statcan.gc.ca. Vitamin D insuff-

iciency was defined as 25-hydroxy vitamin D plasma levels of <50 nmol/L; a cutoff chosen in accordance with the recent Dietary Reference Intakes (DRIs) issued by the Institute of Medicine, which set the new Recommended Dietary Allowance (RDA) for vitamin D based on the maintenance of serum levels >50 nmol/L [16]. This definition of vitamin D insufficiency is in accordance with reports that categorize clinical vitamin D deficiency as ≤ 27.5 nmol/L, insufficiency as ≤ 50 nmol/L, and optimal vitamin D status as ≥ 75 nmol/L, as compared with the traditional definition of optimal status as >50 nmol/L [17,18]. Insulin resistance was estimated from HOMA-IR $[(\text{glucose (mmol/L)} \times \text{insulin } (\mu\text{IU/mL})) \div 22.5]$ [19].

Physical activity was characterized using a measure of the average daily energy expended during leisure time activities reported by the respondent in the past three months. This was the only measure available for the physical activity in the CHMS as it relates to the present study. Smoking was self-reported as: daily, occasional, always on occasions, former daily, former occasional and never smoked. Ethnicity was divided into 12 different groups in the CHMS cohort (Caucasians, Blacks, Koreans, Filipinos, Japanese, Chinese, South Asians, Southeast Asians, Arabs, West Asians, Latin Americans, or others), but for the purposes of this study ethnicity was collapsed into three groups: Caucasians, Asians (*i.e.*, Koreans, Filipinos, Japanese, Chinese, South Asians, Southeast Asians, Arabs and West Asians) and Others (*i.e.*, African Americans, Latin Americans and mixed) in order to allow for comparisons with adequate numbers across groups.

Statistical Analyses

The distribution of relevant variables was examined for outliers or aberrant distributions. Spearman correlation coefficients were estimated between study variables. The relationship between log-plasma vitamin D and the number of metabolic syndrome components was evaluated in a multinomial or ordinal logistic regression model; however, the proportional odds assumption was violated. Therefore, the odds ratio of having metabolic syndrome was modeled as a binary outcome. Plasma vitamin D was categorized using quartiles. Predicted probabilities of case status from the fully adjusted model were estimated. Models were adjusted for physical activity, smoking status, season of interview (to account for seasonality in plasma vitamin D level), age, sex and ethnicity. Information about the latitude was not available. Analyses were conducted among individuals with FPG levels <7 mmol/L and not reporting having been diagnosed with diabetes. The association between plasma vitamin D level and prevalence of metabolic syndrome was exam-

ined among these subjects, effectively excluding individuals considered to have T2DM. Correlations were calculated by Spearman rank correlation coefficient. Sample weighted data were analyzed by SAS 9.3 software (SAS version 9.3, SAS Institute Inc., Cary, NC, USA) using survey-specific procedures and 11 denominator degrees of freedom. To account for the complex design of the CHMS, variance estimates for all measures were generated using bootstrap weights provided by Statistics Canada.

Results

The prevalence of metabolic syndrome, and other characteristics of the study population, is presented in Table 1. Approximately 32% of the study population had one metabolic syndrome component, whereas 8.9% had at least three. The average plasma vitamin D concentration was 67.8 nmol/L in the study population. About 25% of the population was classified as being vitamin D insufficient (<50 nmol/L). The unadjusted average levels of plasma vitamin D in relation to the number of metabolic syndrome components are shown in Figure 1. An inverse relationship was observed between the extent of metabolic syndrome and plasma vitamin D levels ($\rho = -0.1$, $p < 0.0001$). Plasma vitamin D concentrations differed significantly among ethnic groups, with Caucasians having substantially higher serum concentrations than Asians and Others ($p < 0.0001$) (Figure 2).

The association between quartiles of vitamin D and prevalence of metabolic syndrome from an adjusted model is shown in Figure 3. The quartile cutoff values obtained from the data were as follows: ≤ 49.4 (Q1), $>49.4 - 65.8$ (Q2), $>65.8 - 83.1$ (Q3), and >83.1 nmol/L (Q4). Subjects in the third vitamin D quartile had significantly lower odds ratios of having metabolic syndrome, compared to those in the lowest quartile ($OR_{Q3} = 0.45$, 95% CI = 0.21-0.97 and $OR_{Q4} = 0.50$, 95% CI = 0.24-1.06, respectively). A 10 nmol/L increase in vitamin D was associated with a 14% lower odds ratios of having metabolic syndrome ($OR = 0.86$, 95% CI = 0.75-0.99) and vitamin D insufficiency (<50 nmol/L) was associated with an approximately 50% higher odds ratios of having metabolic syndrome ($OR = 1.54$, 95% CI = 1.00-2.38) (data not shown). After adjustment for potential confounders and related lifestyle factors, the probability of having metabolic syndrome was estimated based on the plasma levels of vitamin D (Figure 4). A near linear dose-dependent relationship was observed between vitamin D level and decreasing probability of having metabolic syndrome. The presence of T2DM did not modify this association, as when subjects with FPG >7 mmol/L were included the effect estimates were similar (data not shown). As shown in

TABLE 1. Population characteristics related to metabolic syndrome among Canadians as determined from data from the Canadian Health Measures Survey¹.

Characteristic	n ²	% or mean ⁴	lclm ⁵	uclm ⁵
Sex				
Male	869	49.12	48.55	49.69
Female	949	50.88	50.31	51.45
Age (years)	1818	42.64	42.20	43.08
Age group				
16-35	626	36.04	34.01	38.12
35-65	920	54.09	51.83	56.34
>65	272	9.87	8.91	10.92
Waist circumference (cm)	1805	35.18	34.52	35.84
BMI (kg/m ²)	1,808	26.56	26.01	27.12
HDL-C (mmol/L)	1818	1.34	1.29	1.39
FPG (mmol/L)	1815	4.94	4.88	5.00
Systolic blood pressure (mmHg)	1816	110.74	109.19	112.30
Diastolic blood pressure (mmHg)	1816	70.70	69.63	71.77
Triglycerides (mmol/L)	1,816	1.30	1.20	1.39
No. of metabolic syndrome components				
0	793	42.93	37.07	49.00
1	548	31.77	29.17	34.49
2	307	16.36	13.81	19.28
3+	170	8.93	6.44	12.26
Metabolic syndrome				
No	1648	91.07	87.74	93.56
Yes	170	8.93	6.44	12.26
Vitamin D (nmol/L)	1799	67.80	64.51	71.08
Vitamin D (<50 nmol/L) ³				
No	1348	75.25	69.35	80.33
Yes	451	24.75	19.67	30.65

¹ Studied subjects were selected between 16-79 years of age from the Canadian Health Measures Survey with sampling weights and bootstrap weights for variance applied. The selected 1,818 subjects (unweighted value) represent a weighted value of 24,120,330 Canadians.

² Unweighted frequency

³ Percent of subjects with unknown vitamin D insufficiency was 2.2%

⁴ Weighted measure

⁵ lclm = lower 95% confidence limit; uclm = upper 95% confidence limit

FIGURE 1. Vitamin D plasma levels in relation to the number of metabolic syndrome components (A) and in individuals with and without the disease (B). Number of metabolic syndrome components was inversely correlated with plasma vitamin D level and different between different groups (linear regression, F-test, $\rho = -0.1$, $p < 0.0001$). Plasma vitamin D levels are shown as mean $\pm$ 95% CI. n represents the number of subjects in each category.

FIGURE 2. Plasma vitamin D level stratified by ethnic group. Twelve different ethnic groups were identified from the CHMS: Caucasians, Blacks, Koreans, Filipinos, Japanese, Chinese, South Asians, Southeast Asians, Arabs, West Asians, Latin Americans and others. Ethnic groups were further categorized (see text) as: Caucasians, Asians (i.e., Koreans, Filipinos, Japanese, Chinese, South Asians, Southeast Asians, Arabs and West Asians), and others (Blacks, Latin Americans and mixed). Differences in vitamin D serum levels (95% CI) between groups were statistically significant (linear regression analysis, $p < 0.0001$, F-test). n represents the number of subjects in each category.

FIGURE 3. Odds ratios for the metabolic syndrome in relation to plasma vitamin D levels. Values (95% CI) are adjusted for physical activity, type of smoker, month of interview, age, sex and ethnicity. Quartiles of vitamin D are: ≤ 49.4 (Q1), $>49.4 - 65.8$ (Q2), $>65.8 - 83.1$ (Q3), and >83.1 nmol/L (Q4). The ORs shown here are relative to the lowest quartile (OR_{Q1}=1). Subjects in the third vitamin D quartile had significantly lower odds ratios of having the metabolic syndrome, compared to those in the lowest quartile (OR_{Q3}=0.45, 95% CI= 0.21-0.97 and OR_{Q4}=0.50, 95% CI= 0.24-1.06, respectively, $p < 0.05$). Logistic regression analysis was carried out to test for overall differences between subgroups ($p = 0.23$, F-test). n represents the number of subjects in each category.

FIGURE 5. Insulin resistance (HOMA-IR) across different vitamin D quartiles. Values (95% CI) are adjusted for physical activity, smoking, season of interview, age, sex and ethnicity. Increasing plasma vitamin D level (by 10 nmol/L) was inversely associated with HOMA-IR score ($\beta = -0.08$, $p = 0.006$). HOMA-IR measure was available for 1,689 study subjects (quartiles of plasma vitamin D are stated in Figure 4). Linear regression was carried out for overall difference ($p = 0.031$, F-test). For the number of subjects in each quartile, see Figure 3.

FIGURE 4. A model for risk of the metabolic syndrome as predicted by plasma vitamin D levels. Predicted values are adjusted for physical activity, smoking status, month of interview, age, sex and ethnicity. The Figure shows smoothed regression line for scatterplot of predicted probability of metabolic syndrome by vitamin D serum levels (with 95% CI). A 10 nmol/L increase in vitamin D was associated with 14% lower odds ratios of having the metabolic syndrome (OR=0.86, 95% CI 0.75-0.99). Logistic regression analysis was carried out for overall trend of effect (p for trend = 0.029, Wald chi-square test).

Figure 5, increased plasma vitamin D level (by 10 nmol/L) was inversely associated with HOMA-IR ($\beta = 0.08$, $p = 0.006$) in an adjusted linear model.

Discussion

The present study examined the association between plasma vitamin D, components of the metabolic syndrome and insulin resistance in 1,818 Canadian subjects from the Canadian Health Measures Survey, which represents 24,120,330 Canadians. A strong inverse relationship was observed between plasma vitamin D and the prevalence of metabolic syndrome. In addition, plasma vitamin D was inversely related to the number of metabolic syndrome components. Among people with no components of metabolic syndrome, the average plasma vitamin D concentration was 70.8 nmol/L. In contrast, those with three or more metabolic syndrome components had a significantly lower vitamin D concentration (approximately 60.2 nmol/L) (Figure 1A).

Plasma vitamin D levels predicted the probability of developing metabolic syndrome, as increasing concentrations of vitamin D were linearly and inversely associated with the probability of having this condition. A relationship between vitamin D and metabolic syndrome is further suggested by our

finding of an inverse association between plasma vitamin D and insulin resistance as measured by HOMA-IR. It is known that insulin resistance is a risk factor for later development of T2DM. As shown in Figure 3, individuals in the first vitamin D quartile (<49.4 nmol/L) had a stronger association with the metabolic syndrome than their counterparts in the third and fourth vitamin D quartile (>65.8 and >83.1 nmol/L, respectively). These results, together with the observation that individuals with no metabolic syndrome components had higher vitamin D values (≥ 75 nmol/L, Figure 1A), provide evidence that increased serum vitamin D levels are linked to a lower overall risk of the metabolic syndrome in this population.

Previous studies corroborate results from the present study reporting an association between low vitamin D and the presence of the metabolic syndrome, its related components, and complications. A recent systematic review that examined the relationship between vitamin D serum level and outcomes related to T2DM, hypertension and cardiovascular diseases [5]. Although the review reported a positive association between vitamin D insufficiency and disease risk, the overall conclusion was that, because of heterogeneity across the examined studies, this association was not significant [5]. An inverse, dose-dependent relationship was observed between serum vitamin D and the prevalence of T2DM and metabolic syndrome among adults of several ethnic groups living in the USA [6]. A similar inverse association was observed with insulin resistance and β -cell dysfunction in a population of over 700 Canadian adults at risk for T2DM [20]. In another study of the same population, an association was observed among serum vitamin D and parathyroid hormone and metabolic syndrome [21].

The relationship between vitamin D status and predisposition to metabolic syndrome, insulin resistance and their downstream complications, such as T2DM and cardiovascular disease, may be a result of the immunomodulatory and anti-inflammatory properties of vitamin D. The biologically active form of vitamin D, $1\alpha,25$ -dihydroxyvitamin D ($1,25D$), is known to modulate the production of immunostimulatory cytokines, an effect that is regulated via the vitamin D receptors (VDRs) that exist in a variety of immunity-related cell types [22]. Furthermore, VDRs are present in pancreatic β -cells, and $1,25D$ is known to stimulate insulin production and secretion in these cells [24]. In addition to its direct effects on insulin output, vitamin D-mediated down-regulation of the production of pro-inflammatory cytokines has been shown to improve insulin sensitivity, an effect mediated by interaction with vitamin D response elements (VDRE) present in the promoter region of cytokine-encoding genes. This interaction down-regulates the transcriptional activities of cytokine genes

and, subsequently, the synthesis of pro-inflammatory factors. The effect of genetic factors along the vitamin D signaling pathway on the risk of metabolic syndrome and T2DM has been substantiated from research showing that a *VDR* gene polymorphism is associated with disease risk [23].

Metabolic syndrome and insulin resistance are highly prevalent in North America and can be considered as early stages in the onset of frank T2DM and cardiovascular disease. These chronic conditions pose a significant burden on health care systems worldwide, and their prevalence is higher among certain ethnic groups. Therefore, it is critical to devise population-based intervention strategies that are at low-cost, effective and have no to minimal side effects. Such interventions may also target "high-risk" sub-populations and ethnic groups. In this context, our results reveal that Asians, in general, have the lowest levels of serum vitamin D among the ethnic groups examined here. Canadians with an Asian origin may, therefore, benefit from a targeted approach employing vitamin D supplementation for the intervention of the metabolic syndrome and related conditions. Furthermore, given that the prevalence of vitamin D insufficiency (<50 nmol/L) in Canada is high [12] and that an optimal vitamin D status can be implicated in a reduced risk of metabolic syndrome and insulin resistance, as demonstrated in this study, intervention strategies based on increasing vitamin D serum levels in "at-risk" group may not only represent an effective strategy to reduce the prevalence of the condition in vulnerable sub-populations but also in the general Canadian population. This approach may accompany the traditional intervention strategies (e.g., weight loss, exercise and dietary modification) to improve the outcome of these approaches [24].

The present study has several limitations. The potential for residual confounding from measured sources, as well as unknown confounding from dietary or other sources, may have affected our observed relationships, *i.e.*, between vitamin D levels and the presence of metabolic syndrome. Furthermore, this analysis was cross-sectional in nature and therefore we are unable to make any inferences about causality based on the associations observed here. Biologically, vitamin D may down-regulate immune responses that, subsequently, initiate complex downstream molecular and cellular processes leading to the later development of the metabolic syndrome, T2DM and cardiovascular disease; however, given the central role of obesity in the metabolic syndrome, the apparent association of vitamin D insufficiency with metabolic syndrome may result from its sequestration, as a fat-soluble micronutrient, in adipose tissue in obese individuals [25]. Furthermore, it is well known that low vitamin D leads to elevated levels of parathyroid hormones

(PTH) and then to increased calcium in the adipocytes, which, in turn, could influence lipogenesis and adiposity [21]. While there have been a few randomized controlled trials assessing the possible causal relationship between vitamin D and cardiometabolic health measures, the evidence from such studies has been equivocal [26]. Finally, 82% of our study subjects were Caucasian. This distribution is representative of the general Canadian population; however, the lack of ethno-cultural diversity may limit broadening our findings to encompass other ethnic groups. It may be invalid to extrapolate the association between vitamin D and the risk of metabolic syndrome observed in the present study to ethnic groups identified as "at-risk" for T2DM and cardiovascular disease, such as Asians [8] and Aboriginals [18].

In conclusion, the present study demonstrates the first observation of an association between plasma vitamin D level and the extent (implicated by the number of metabolic components) of metabolic syndrome and insulin resistance in Canadians, and that this likelihood is further increased as plasma vitamin D levels decrease. The study highlights the need for adequately powered randomized controlled clinical trials to evaluate the value of replenishment of vitamin D on the metabolic syndrome as an approach for an effective population-based strategy for disease prevention.

Acknowledgments

We thank Drs. Margaret de Groh and Linda Greene-Finestone of the Public Health Agency of Canada for comments on the early drafts of the manuscript. AE-S holds a Canada Research Chair in Nutrigenomics. DRB, PA, BG-B, HM, MK and AB are supported by the Public Health Agency of Canada.

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