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Revisión

Dairy products consumption versus type 2 diabetes prevention and treatment; a review of recent findings from human studies

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Abstract

Introduction: **It has been claimed that the appropriate consumption of dairy products can be beneficial for the prevention and treatment of type 2 diabetes mellitus (T2DM).**

Objective: **The objective of this review is to critically analyze the main scientific evidence about this topic.**

Methods: **MEDLINE, PubMEd, Science Direct, SCIELO and LILACS were searched for studies published over the past 12 years exploring the effects of the consumption of dairy products or its components (calcium, vitamin D and magnesium) on T2DM.**

Results and discussion: **Epidemiological studies indicate that consumption of at least three servings of low-fat dairy products per day as a part of a healthy diet is crucial to reduce the risk of developing T2DM. The majority of the analyzed intervention studies reported beneficial effects of increased calcium and vitamin D ingestion on insulin sensitivity improvement and T2DM prevention.**

Conclusions: **Although the impact of dairy consumption to treat T2DM needs further investigation, the consumption of low-fat dairy products may be an important strategy to prevent and control T2DM.**

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Key words: *Dairy products. Milk. Calcium. Vitamin D. Diabetes. Insulin resistance.*

CONSUMO DE LOS PRODUCTOS LÁCTEOS *VERSUS* PREVENCIÓN Y TRATAMIENTO DE LA DIABETES TIPO 2; UNA REVISIÓN DE LOS RESULTADOS RECIENTES DE ESTUDIOS EN HUMANOS

Resumen

Introducción: **Se ha afirmado que el consumo adecuado de los productos lácteos puede ser beneficioso para la prevención y el tratamiento de la diabetes mellitus tipo 2 (DMT2).**

Objetivos: **El objetivo de esta revisión es analizar críticamente la principal evidencia científica sobre este tema.**

Métodos: **MEDLINE, PubMed, Science Direct, SCIELO y LILACS fueron consultadas para estudios publicados en los últimos 12 años explorando los efectos del consumo de productos lácteos o sus componentes (calcio, vitamina D y magnesio) en la DMT2.**

Resultados y discusión: **Los estudios epidemiológicos indican que el consumo de por lo menos tres porciones de productos lácteos bajos en grasa al día como parte de una dieta saludable, es crucial para reducir el riesgo de desarrollar DMT2. La mayoría de los estudios de intervención analizados reportaron efectos benéficos del aumento del calcio y de la ingestión de vitamina D en la mejora de la sensibilidad a la insulina y la prevención de DMT2.**

Conclusiones: **Aunque el impacto del consumo de productos lácteos para tratar DMT2 necesita más investigación, el consumo de productos lácteos bajos en grasa puede ser una importante estrategia para prevenir y controlar la DMT2.**

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Palabras clave: *Productos lácteos. Leche. Calcio. Vitamina D. Diabetes. Resistencia a la insulina.*

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Introduction

Type 2 diabetes mellitus (T2DM), which is partially characterized by insulin resistance (IR), is one of the most common chronic diseases in the world. IR is a pathological condition in which insulin becomes less effective at lowering blood glucose levels. T2DM occurs when the functional expansion of islet β-cells fails to compensate for the degree of IR.[1] The worldwide prevalence of this disease among adults is estimated to increase from 285 million cases (6.4% of the population) in 2010 to 439 million (7.7%) in 2030. It is believed that this increase will be especially prominent in developing countries (69% increase compared to an increase of 20% in developed countries).[2]

The rapid increase in the incidence of T2DM indicates a low correlation with genetic causes and a strong correlation with lifestyle and/or environmental factors.[3,4] Accordingly, body weight reduction, increased physical activity, and good dietary habits are effective strategies for reducing the incidence of IR and T2DM[5-7] as well as for treating these disorders.[8,9] With regard to dietary habits, the influence of dairy intake on the prevention and treatment of T2DM deserves special attention.[10]

Although several epidemiological studies[11-26] have reported that the consumption of dairy products or their components may reduce the risk of developing T2DM, this effect was not considered in the new Dietary Reference Intakes (DRIs).[27] Dairy products are the best nutritional sources of calcium. Fortified dairy products are considered a good source vitamin D. Thus, the effect of dairy intake on the manifestation and control of T2DM reflects the synergistic effect of these two components,[28] and the benefits of dairy intake have been attributed to both calcium and vitamin D. It has been claimed that the inconsistency in the results of a small number of randomized clinical trials does not allow the establishment of a causal relationship between dairy product consumption and the suggested benefits.[27]

The objective of this study was to critically analyze the major scientific evidence regarding the role of dairy products and their components in the prevention and management of T2DM. We believe this is an important step to stimulate the conductance of scientific studies on this topic, favoring the establishment of public policies that can lead to health benefits to the world's populations.

Methods

We searched the MEDLINE, PubMEd, Science Direct, Scientific Electronic Library Online (SCIELO), and Latin American and Caribbean Health Sciences Literature-LILACS electronic databases to identify studies published within the last 12 years regarding the effects of consuming dairy products or their components (calcium, vitamin D and magnesium) on T2DM. For epidemiological studies, the prevalence and risks of T2DM and/or insulin resistance syndrome (IRS) were considered regarding dairy products, calcium and vitamin D consumption. For intervention studies, a minimum of 4 weeks intervention was considered regarding dairy products consumption, supplementation level (minimum) of vitamin D (400 IU) and calcium (500 mg), in which fasting glycemia and insulinemia, glycated hemoglobin, Homeostasis Model Assessment (HOMA) index, HOMA of insulin resistance (HOMA-IR), HOMA of insulin sensitivity (HOMA-%S); HOMA of β-cell function (HOMA-%B), quantitative insulin sensitivity check index (QUICKI) and intraplatelet calcium were assessed.

The studies were searched using the following main terms: dairy product, milk, diabetes, IR, glucose intolerance, impaired glucose, calcium, vitamin D, dairy products consumption, and serum vitamin D.

The effects of dairy intake on T2DM prevention and treatment

Evidence from epidemiological studies

The results of several epidemiological studies substantiate the existence of an inverse correlation between the consumption of dairy products, calcium, and/or vitamin D and T2DM[11-15,17-22,24] or IRS.[12,17,18,20,23-26]

The results of studies involving the participation of men or women indicated that each daily dairy portion consumed reduced the risk of developing T2DM by 9%[11] and 4%[13] in males and females, respectively. The consumption of ≥ 2.9 dairy portions per day protected against T2DM compared to < 0.9[11] and < 0.85[13] dairy portions daily for males and females, respectively. The results of these two studies suggest that dairy products prevent T2DM to a greater extent in males compared to females.[11,13] The higher testosterone secretion by men can lead to a higher waist-to-hip fat concentration, which in turn may favor an increase in visceral adiposity.[29] It has been proposed that this type of adiposity is associated with both peripheral and hepatic IR in T2DM.[30] Furthermore, the consumption of dairy products has a most pronounced effect on abdominal fat than on deep subcutaneous adipose tissue.[31,32] It is possible, therefore, that the consumption of dairy products by men was more effective on reducing the risk of T2DM because they had greater accumulation of visceral fat than women.

It is noteworthy that the best effects were associated with the consumption of low-fat dairy products.[11,13,21,22] No beneficial effects were verified for subjects who consumed the high-fat ones.[21,22] It was observed that while the consumption of one dairy portion daily resulted in an average reduction of 5% in the risk of T2DM in both males and females, the consumption of one portion of low-fat dairy products was associated

with a 10% reduction.[22] In postmenopausal women, an average daily intake of at least 1.5 low-fat dairy portions reduced the risk of T2DM compared to those with a daily intake of < 0.5 portions, especially among women with a higher BMI.[21]

In contrast, the authors of a recent study did not observe any beneficial effect of dairy consumption on T2DM prevention, regardless of its fat content. A total of 4,526 men and women were involved in that 10-year prospective study.[33] However, the data obtained in that study was analyzed after being divided into tertiles instead of quintiles as it has been done in other studies. Due to that the small variation in the dairy intake among groups (difference of 329 g/day between the medians of the first and third tertiles) may have impaired the detection of significant correlations. In addition, the average values of dairy (246 g/day) and calcium (935 ± 321 mg/day) intake in the group with the lowest intake level were still relatively high. It seems that the increased risk of T2DM occurs mainly when dairy consumption is lower than those reported in the aforementioned study.[24]

The beneficial effects of calcium and vitamin D intakes on the risk of developing T2DM were assessed in three prospective studies.[14,15,19] The authors of two of these studies did not identify significant effects of calcium[19] or vitamin D[14] consumption, although Pittas et al.[14] and Van Dan et al.[15] reported that calcium alone did have an effect. In the latter study, this effect was observed before adjusting for magnesium intake. Magnesium acts as a cofactor of enzymes involved in glucose metabolism. Low magnesium intake has been associated with an increased risk of T2DM.[34] Since dairy products are good sources of magnesium, this element may be implicated in the benefits associated with dairy consumption. Vitamin D was shown to play an important role in reducing the T2DM risk only among the participants who used supplements of this vitamin.[14] However, a high calcium intake significantly reduced the risk of developing T2DM in participants who consumed the greatest levels of dietary vitamin D.[19] The intake of doses greater than 1,200 mg/day of calcium and 800 IU/day of vitamin D correlated with a 33% reduction (RR 0.67, CI, 0.49-0.90) in the risk of T2DM compared to doses of less than 600 mg/day and 400 IU/day, respectively.[24] Such results are surprising from a clinical perspective due to the magnitude of the reduction of the risks.

The effects of the consumption of dairy products or their components on T2DM and IRS was investigated in two meta-analyses.[18,24] The results of these studies confirmed the protective effect of dairy product, calcium, and vitamin D intake. The authors of the first study[18] reported 10% (RR 0.92; CI, 0.86-0.97) and 25% (RR 0.74; CI, 0.64-0.84) reductions in the probability of developing T2DM and IRS, respectively, with highest intake of milk or dairy products. In the second study,[24] the consumption of 3 to 5 portions of dairy products per day reduced the probability of developing T2DM (OR 0.86; CI, 0.79-0.93) and IRS (OR 0.71; CI 0.57-0.89) compared to the intake of less than 1.5 portions per day.

Among the studies that assessed the effect of dairy products on T2DM and IRS,[12,20,23,25,35] two reported protective effects against T2DM and IRS,[12,20] two observed this effect only for IRS,[23,25] and one reported that dairy consumption did not affect the risk of either T2DM or IRS.[35] Among the studies that investigated only the effect of dairy products on IRS,[17,26,36,37] the authors of three of these studies found a protective effect[17,26,36] and one did not.[37] However, the study conducted by Snijder et al.[37] only assessed dairy intake at baseline. Therefore, one cannot guarantee that the dietary patterns of the participants remained the same during the 6.4 years of follow-up. It should be noted also that the study population was relatively healthy, which might have contributed to the lack of correlations.

The conflicting results of an additional study also deserve discussion. Lawlor et al.[35] reported lower HOMA scores, triglyceride concentrations, BMI values, and high-density lipoprotein (HDL) levels among women who reported that they never drank milk compared to those that did. This study included 4,024 British postmenopausal women aged 60 to 79 years old. The probability of developing IRS was 45% lower among women who never drank milk compared to those who did (OR 0.55; CI, 0.33-0.94), even after adjusting for interfering variables. The authors of that study emphasize the need to establish whether there is causal relationship between the investigated variables and discuss the possibility that a biological variable, such as lactose intolerance, may have interfered with the results. Non-diabetic individuals are more prone to lactose intolerance and thus exclude dairy products from their diet. Therefore, the protective effect associated with the non-consumption of dairy products verified in their study may have been related with a lower genetic susceptibility to T2DM. In that case, the results obtained in that study would not indicate the lack of a protective effect of dairy intake.

Although the results of most studies indicate the existence of an inverse correlation between T2DM and dairy consumption, the results of some studies are conflicting.[23,25,35,37] Factors that may have interfered with the magnitude of the obtained correlations include gender, age range, ethnicity, BMI, and the amount and type of dairy products consumed. In some prospective studies,[13,15,19,25,33,37] dietary intake was not monitored throughout the study. In other studies,[18,21,26] the exact amounts of dairy products and/or calcium and vitamin D consumed were not described or adjustments were not consistently performed among the assessed groups to account for confounding variables. The main characteristics and results from epidemiological studies in which the effect of the consumption of dairy products, calcium, and/or vitamin D on the development of T2DM and IRS are described in table I and table II, respectively.

Table I
Epidemiological studies which assessed the effect of dairy intake on T2DM

Type of study	*First author (year)[ref.]*	*n*	*Gender*	*Sample characteristics*		*Indicator*	*Studied factor*	*Main results*
				Age (mean/interval)	*Other*			
Prospective	Choi et al. (2005)[11]	41,254	M	40-75 y (onset)	Healthcare professionals without diabetes, CVD, or cancer	Consumption of dairy, LFD, and HFD	Risk of T2DM	– Consuming ≥ 2.9 portions/day resulted in a lower risk of T2DM than consuming ≤ 0.9 portion – Each consumed portion decreased the risk of T2DM by 9%; the decrease in risk was higher for LFD
	Liu et al. (2006)[13]	37,183	F	55 y (onset)	Without diabetes, CVD, or cancer	Consumption of dairy, LFD, and HFD	Risk of T2DM	– Consuming > 2.9 portions/day associated with lower T2DM risk than consuming < 0.85 portions – Each portion consumed/day reduced the risk of disease by 4% – Better results observed with LFD
	Pittas et al. (2006)[14]	83,779	F	30-55 y (onset)	Without diabetes, CVD or cancer	Dietary or supplemental calcium and vitamin D consumption	Risk of T2DM	– No correlation between vitamin D consumption and T2DM – High calcium doses (> 500 mg/day) and vitamin D (> 400 IU/day) correlated with reduced risk of T2DM – Total calcium intake > 1,200 mg/day: lower risk of T2DM than ≤ 600 mg/day; Intake > 1,200 mg/day of calcium and > 800 IU/day of vitamin D: reduced the risk of T2DM by 33% (compared to < 600 mg/day of calcium and < 400 IU of vitamin D)
	Van Dan et al. (2006)[15]	41,186	F	21-69 y (onset)	Black women Without diabetes	Dietary calcium consumption	Odds of developing T2DM	– Reduced risk of T2DM in the highest calcium intake quintile (median: 661 mg/day) compared to the lowest (219 mg/day) – No correlation with calcium intake after adjusting for Mg – Consumption of LFD reduced the risk of T2DM compared to consumption < 1 portion/day
	Elwood et al. (2007)[25]	2,375	M	45-59 y (onset)	Without diabetes	Dairy and/or milk consumption	Odds of developing T2DM and IRS	– No correlation between milk consumption and T2DM – Odds for IRS at baseline: lower in subjects who consumed ≥ 1 cup or more of milk or other dairy products
	Kirii et al. (2009)[19]	59,796	M/F	45-74 y (onset)	Japanese without CVD, CVD, CLD, or CKD	Dietary dairy, calcium, and vitamin D consumption	Odds for developing T2DM	– Calcium did not reduce the odds of developing T2DM – Intake of high levels vitamin D and calcium: reduced risk for T2DM – Dairy intake: lower odds of T2DM in women

Table I *(cont.)*
Epidemiological studies which assessed the effect of dairy intake on T2DM

Type of study	*First author (year)[ref.]*	*n*	*Gender*	*Sample characteristics*		*Indicator*	*Studied factor*	*Main results*
				Age (mean/interval)	*Other*			
Prospective	Fumeron et al. (2011)[20]	3,435	M/F	30-65 y (onset)	–	Dairy consumption (milk, cheese, and other)	Odds for developing T2DM, IRS, or hyperglycemia	– Consumption of other dairy products (except cheese) and total calcium consumption: inverse correlation with incidence of T2DM, IRS, and fasting hyperglycemia – Cheese consumption: inverse correlation with IRS
	Margolis et al. (2011)[21]	82,076	F	50-79 y (onset)	Postmenopausal women Ethnic diversity	Dairy, LFD, and HFD consumption	Risk of T2DM	– Consumption of > 1.5 regular dairy portions/day: reduced the risk of T2DM, especially among women with the highest BMI values – Consumption of FRD did not have a similar effect
	Soedamah-Muthu et al. (2012)[33]	4,526	M/F	56 y (onset)	Mostly Caucasian	Dairy, LFD, and HFD consumption	Risk of T2DM	– Inconsistent correlation with T2DM incidence
Meta-Analysis	Pittas et al. (2007)[16]	–	–	–	–	Dairy, calcium and vitamin D consumption	Odds of developing T2DM and IRS	– High calcium doses (661-1,200 mg/day)+vitamin D reduced the odds ofT2DM compared to low doses (219-600 mg/day) – Consumption of 3 to 5 dairy portions/day reduced the odds for T2DM compared to intake of 1.5 portions – Consumption of 3 to 4 dairy portions/day reduced the odds for IRS compared to intake of 0.9-1.7 portions/day
	Elwood et al. (2008)[18]	–	–	–	–	Dairy intake	Risk of T2DM and IRS	– Approximate 10% reduction of T2DM risk in response to high dairy intake – Consumption of more dairy amounts reduced the risk of IRS
	Song et al. (2011)[22]	–	–	–	–	Dairy, LFD, and HFD consumption	Risk of T2DM	– Consumption of dairy products: 14% reduced risk of T2DM; the effect was higher with LFD (RR: 0.82; CI: 0.74-0.90) and absent with FRD – Each dairy portion consumed/day is associated with a 5% decrease in T2DM risk (10% for LFD)

M: Male; F: Female; T2DM: Type 2 diabetes mellitus; BMI: Body mass index; CI: Confidence interval; CLD: Chronic liver disease; CKD: Chronic kidney disease; CVD: Cardiovascular disease; HFD: High-fat dairy products; FM: Fermented milk; WC: Waist circumference; IRS: Insulin resistance syndrome; LFD: Low-fat dairy products; RR: Relative risk; Vit D: Vitamin D; MS: Metabolic syndrome.

Table II
Epidemiological studies which assessed the effect of dairy intake on IRS

Type of study	*First author (year)[ref.]*	*n*	*Sample characteristics*		*Other*	*Indicator*	*Studied factor*	*Main results*
			Gender	*Age (mean/interval)*				
Prospective	Pereira et al. (2002)[36]	3,157	M/F	18-30 y (onset)	Caucasian and black	Dairy consumption	Odds of developing IRS	– Dairy intake > 35 times/week reduced the odds in 72 overweight individuals for developing IRS compared to similar individuals who consumed dairy < 10 times/week – No correlation observed in individuals with normal weight – Each additional episode of dairy consumption reduced the odds of IRS by 21% – The results were similar for both sexes and races and were not affected after adjustment for other dietary components
Cross-sectional	Azadbakht et al. (2005)[23]	827	M/F	18-74 y	Without diabetes, CVD, or stroke	Dairy consumption	Odds of developing IRS components	– No effect on fasting glycemia – Consumption of ≥3.1 dairy portions/day: lower odds of increased WC, hypertension, and IRS than consumption of < 1.7 portions/day
	Ruidavets et al. (2007)[26]	912	M	45-64 y	–	Dairy intake	Odds of developing IRS	– Prevalence of IRS: 32.6% for the lowest *vs.* 19.9% for the highest dairy intake – Decreased odds for IRS in the greatest dairy intake quintile compared to the lowest
	Kelishadi et al. (2008)[17]	4,811	M/F	6-18 y	Students	Dairy intake	Odds of developing IRS	– Dairy intake reduced the odds for developing IRS in boys
	Snijder et al. (2008)[37]	1,124	M/F	50-75 y (onset)	Use of medication Caucasian	Dairy intake	Odds of developing IRS	– No significant correlation between dairy intake and IRS parameters

M: Male; F: Female; T2DM: Type 2 diabetes mellitus; BMI: Body mass index; CI: Confidence interval; CLD: Chronic liver disease; CKD: Chronic kidney disease; CVD: Cardiovascular disease; HFD: High-fat dairy products; FM: Fermented milk; WC: Waist circumference; IRS: Insulin resistance syndrome; LFD: Low-fat dairy products; RR: Relative risk; Vit D: Vitamin D; MS: Metabolic syndrome.

Evidence from intervention studies

The causal relationship between the consumption of dairy products or their components and the development and treatment of T2DM can only be evaluated by intervention studies. There is only one clinical trial where dairy foods have been used as the experimental variable with respect to the treatment of T2DM in humans.[38] The remaining eight studies used supplements (pills or powders) containing nutrients like calcium and/or vitamin D found in dairy products (table III).

The effects of oral calcium supplements on insulin sensitivity were assessed in a parallel randomized controlled single-blinded trial.[39] Hypertensive patients with T2DM (n = 15) were given 1,500 mg of oral elemental calcium daily (as calcium lactate gluconate and calcium carbonate pills) or no supplements for 8 weeks. Higher insulin sensitivity was observed in the calcium supplemented group compared to the non-supplemented group. Fasting glycemia, insulinemia, and glycosylated hemoglobin (HbA1c) levels were not significantly affected. Although the sodium-hydrogen exchange (NHE-1) activity was reduced in the supplemented group, this change was not correlated with a change in insulin sensitivity. However, a significant reduction in intraplatelet calcium concentrations was observed in the supplemented group. The authors also verified the occurrence of a positive correlation between the intraplatelet calcium concentrations and changes in insulin sensitivity. Increased intraplatelet calcium concentrations are considered a common characteristic of T2DM, hypertension, and obesity.[40,41] The study results suggest that daily supplementation with 1,500 mg of calcium may reduce intraplatelet calcium concentration levels and improve insulin sensitivity in diabetic and hypertensive patients. However, it is noteworthy that these patients exhibited some extent of IR in addition to a high basal intraplatelet calcium concentration. It is not known whether similar results would also occur in individuals with lower levels of IR.

The combined effects of calcium and vitamin D supplements were studied in four intervention studies.[16,38,42,43] In a factorial clinical trial,[38] individuals with T2DM consumed yogurt-based beverages with different levels of calcium and vitamin D over 12 weeks. The participants were randomly allocated to 3 groups that drank one of the following beverages: plain yogurt without vitamin D_3 and with 150 mg Ca/250 mL (PY), yogurt fortified with 500 IU vitamin D_3 and 150 mg Ca/250 mL (DY), and yogurt fortified with 500 IU vitamin D_3 and 250 mg Ca/250 mL (DCY). Vitamin D_3 serum levels were significantly increased in the DY and DCY groups. HOMA-IR scores and fasting glycemia were significantly decreased in both groups compared with PY, but were lower in the DY group. However, the insulinemia and HbA1c levels did not differ between the groups.

The results of the previously mentioned study[38] suggest that the daily intake of vitamin D_3-fortified yogurt with or without the addition of calcium may improve insulin sensitivity (HOMA-IR) and reduce fasting glycemia in diabetic individuals. However, it is not known whether the changes observed during the 12 week-study would persist if the beverages were consumed for a longer period of time. It should be noted that since the yogurt was not consumed in the laboratory, it is impossible to confirm whether the study treatments were actually consumed by subjects. Regardless, the results suggest that increased vitamin D intake may be beneficial in preventing and controlling T2DM.

Elderly volunteers with normal fasting glucose or impaired fasting glucose (IFG) were given calcium pills (500 mg calcium citrate) and vitamin D (700 IU vitamin D_3) or placebo for 3 years. The IFG group exhibited smaller increases in fasting glycemia (+0.02 ± 0.4 *vs.* + 0.34 ± 6.1 mmol/L, P = 0.042) and HOMA-IR scores (+0.05 *vs.* +0.91, P = 0.031) compared to the placebo group.[16]

De Boer et al.[42] conducted a randomized double-blind clinical trial involving the participation of 33,951 healthy women who were given daily supplements of calcium (1,000 mg calcium carbonate) and vitamin D_3 (400 IU) or placebo for seven years. The incidence of diabetes in the study population was 6.5%. Supplementation did not alter the fasting glycemia, insulinemia, or HOMA-IR scores. One caveat of this study is that the participants reported if they were diabetics or not. No test was done to confirm the occurrence of diabetes among the participants. T2DM can manifest many years prior to a formal diagnosis.[44] The lack of homogeneity in the health status of those participants at the beginning of the study may have impaired the results.

The effects of vitamin D supplementation with or without calcium over 16 weeks were assessed in a study involving 92 adults.[43] The participants were divided into two groups: one group was supplemented daily with vitamin D_3 (2,000 IU or 50 mcg), and the other group received a placebo. Half of each group also received calcium supplements (800 mg calcium carbonate). Insulin secretion and sensitivity increased in the group exclusively supplemented with vitamin D compared to the placebo. Calcium supplementation did not affect any of the measured parameters.

Two other double-blind studies tested the effect of vitamin D supplements were tested in non-diabetic, overweight subjects.[45,46] Postprandial insulin sensitivity significantly improved following the administration of 120,000 IU of vitamin D_3 every two weeks over a six-week period.[45] The authors of another study reported that improved insulin sensitivity and reduced fasting glycemia were observed in subjects who took daily supplements of 100 mcg (4,000 IU) of vitamin D_3 for six months.[46] These findings further confirm that vitamin D might be important in the prevention and control of T2DM.

Conversely, daily vitamin D_3 supplements (83.3 mcg/ 3,332 IU) for 12 months did not have any benefi-

Table III
Interventional studies of dairy, calcium and vitamin D intake on IRS and T2DM

First author (year)[ref.]	*Type of study*	*Subjects*	*n*	*Gender*	*Age (mean or range)*	*Time*	*Study design and doses*	*Main study results*	*Improvement on IS*
Pittas et al. (2007)[16]	Double-blinded	Non diabetic	314	M/F	71 y	3 y	500 mg of calcium citrate plus 700 IU of vitamin D per day and placebo group. There were two subgroups within: normal fasting glucose group (NFG) and impaired fasting glucose group (IFG).	$25(OH)D_3$ increased and of PTH level decreased in the treatment group. In IFG fasting plasma glucose had lower increase compared with placebo group and lower increase in HOMA-IR.	Yes
De Boer et al. (2008)[42]	Double-blinded	Self-reported no diabetes	33,951	F	62 y	7 y	1,000 mg of calcium carbonate plus 400 IU of vitamin D3 daily or placebo group.	Cumulative incidence of diabetes: 6.5%. In the supplementation group $25(OH)D_3$ concentrations was 23 nmol/L higher than placebo. Fasting glucose, insulin concentrations and HOMA-IR were not affected in the study.	No
Jorde and Figenschau (2009)[48]	Single-blinded placebo	Type 2 diabetic	36	M/F	56.2 ± 7.8 y	6 mo	Placebo group or vitamin D supplementation (40,000 IU of cholecalciferol) weekly.	Fasting glucose, insulin HOMA-IR and HbA1c were not affected compared to baseline within groups or compared with placebo. In supplementation group $25(OH)D_3$ was higher and PTH was lower.	No
Nagpal et al. (2009)[45]	Double-blinded placebo	Non diabetic obese	65	M	43.5 ± 7.5 y	6 wk	Placebo group and supplement group receiving 3 doses of 120,000 IU of vitamin D3 at fortnightly intervals.	$25(OH)D_3$ levels increased, PTH levels decreased, oral glucose insulin sensitivity increased in the supplement group, and decreased in the placebo group. Quantitative insulin sensitivity check index, HOMA-IR and β cell function remained unaffected.	Yes
Pikilidou et al. (2009)[39]	Single-blinded	Type 2 DM Hypertension	31	M/F	59 ± 7.9 y	8 wk	1,500 mg of calcium orally daily and placebo group.	At the end of the study insulin sensitivity was higher, intraplatelet calcium and NHE-1 activity were lower in the treatment group.	Yes

Table III *(cont.)*
Interventional studies of dairy, calcium and vitamin D intake on IRS and T2DM

First author (year)[ref.]	*Type of study*	*Subjects*	*n*	*Gender*	*Age (mean or range)*	*Time*	*Study design and doses*	*Main study results*	*Improvement on IS*
Von Hurst et al. (2009)[46]	Double-blinded placebo	Non diabetic	81	F	41 ± 9.6 y	6 mo	2 groups: placebo and the vitamin D group (100 mcg (4,000IU) of cholecalciferol (D3) per day).	Insulin sensitivity (HOMA-IR) decreased, HOMA %S increased, fasting insulin declined and overall IR decreased compared with baseline in the supplement group. Serum 25(OH)D_3 increased at 3 months and declined at 6 months. Fasting glucose, HOMA %B were not affected.	Yes
Zitterman et al. (2009)[47]	Double-blinded placebo	Healthy overweight	165	M/F	48.1 ± 10.2 y	12 mo	During weight-loss-placebo group and the vitamin D group (83.3 mcg (3,332 IU) of cholecalciferol daily).	Weight loss was not affected by vitamin D supplementation. 25(OH)D_3 and calcitriol concentrations increased in the vitamin D group. Fasting serum glucose, proinsulin and HbA1c were not altered.	No
Nikooyeh et al. (2011)[38]	Factorial	Type 2 DM	90	M/F	50.7 ± 6.1 y	12 wk	Groups-consumption twice a day: 1) plain yogurt with no vitamin D and 150 mg Ca/250 ml; 2) vitamin D fortified yogurt drink with 500 IU of vitamin D_3 and 150 mg Ca/250 ml; 3) vitamin D with calcium fortified yogurt drink, containing 500 IU of vitamin D_3 and 250 mg Ca/250 ml.	Fasting glucose, insulin, HOMA-IR and HbA1c-lower on groups 2, 3 than group 1. 25(OH)D_3-higher on groups 2 and 3.	Yes
Mitri et al. (2011)[51]	Double-blinded placebo	Non diabetic at high risk of type 2 DM	92	M/F	57 ± 1 y	16 wk	2 groups: 2,000 IU (50 mcg) of vitamin D_3 /day or placebo, within each group: 800 mg/day of calcium carbonate or placebo.	Disposition index increased in the vitamin D group and decrease in no vitamin D group. Insulin secretion improved in the vitamin D group. Calcium did not affect any of the assessed outcomes.	Yes

M: Male; F: Female; y: Years; wk: Weeks; mo: Months; IS: Insulin sensitivity; IR: Insulin resistance; NHE-1: Sodium-hydrogen exchanger activity; NFG: Normal fasting glucose; IFG: Impaired fasting glucose; Ca: Calcium; 25(OH)D_3: 25-hydroxyvitamin D3; PTH: Parathormone; HOMA: Homeostasis model assessment; HOMA-IR: Homeostasis model assessment of insulin resistance; HOMA %S: Homeostasis model assessment of insulin sensitivity; HOMA %B: Homeostasis model assessment of β-cell function; QUICKI: Quantitative insulin sensitivity check index; HbA1c: Glycated hemoglobin %.

cial effect in overweight or obese subjects[47]. A 6-month regimen of weekly vitamin D_3 supplementation of 40,000 IU (5,700 IU per day in capsule form) did not affect the fasting glycemia, insulin, HOMA-IR scores, or HbA1c levels in diabetic subjects.[48]

All of the studies that assessed the effects of vitamin D[16,38,42,43,45-49] reported significant increases in 25(OH)D_3 serum levels, which may subsequently improve insulin sensitivity.[50-52] Nevertheless, the variation among the supplement doses (ranging from 400 to 8,000 IU/daily) and the amounts of vitamin D typically found in dairy products (40 to 100 IU/milk or yougurt serving, best described later) must be taken into account. Moreover, the previously mentioned studies focused on the effect of vitamin D supplements in Caucasians, and even after adjusting for ethnicity, the results cannot be extrapolated to darker skin people, in whom vitamin D synthesis is impaired by greater skin pigmentation.[53] In addition, the geographical locations where the studies were conducted play a role in the extent of solar exposure and skin synthesis of vitamin D. These variables make it difficult to apply the findings of this study to populations that live at different latitudes.

Although several authors have reported that calcium improves insulin sensitivity and glycemia,[16,39,42] others have reported the lack of such effect.[42,43] Therefore, additional intervention studies are needed to elucidate the effects of calcium on glycemic status and insulin sensitivity in both normoglycemic and diabetic individuals.

Actual nutritional recommendations *vs.* scientific evidences regarding dairy consumption and T2DM

The new DRIs for calcium and vitamin D were published in 2011.[27] The greatest difference from the previous DRIs was a change from Adequate Intakes (AI) to Estimated Average Requirements (EAR), Recommended Dietary Allowance (RDA), and Tolerable Upper Intake Level (UL).[54] Based on recent scientific studies about effects of calcium and vitamin D on bone health, an expert panel established by the Institute of Medicine (IOM) defined the reference values for several age ranges. The EAR and RDA of calcium for individuals > 1 year old ranges from 500-1,100 mg/day and 700-1,300 mg/day, respectively. Vitamin D levels were determined assuming low solar exposure levels. The EAR for individuals > 1 year old corresponds to 400 IU/day. The vitamin D RDA values differ by age group, and are listed as 600 IU/day for people between 1 and 70 years old and 800 IU/day for those > 71 years old and older.[27]

Dietary guidelines (DGs) are a primary nutritional educational tool with a pivotal role in translating nutrient recommendations into food intake recommendations for the general population.[55] DGs must comply with the RDA,[55] which meets the needs of 97.5% of the healthy population.[27] One dairy portion supplies an average of 300 mg of calcium. Therefore, the calcium recommendations for adults (1,000-1,300 mg/d) are not met when < 3 dairy portions per day are consumed per day, even when other dietary calcium sources are consumed. For this reason, the daily dairy intake recommendations were increased from 2-3 portions to at least 3.[55,56]

The vitamin D content of dairy products depends on whether the products are fortified. Vitamin D is heat stable, and thus, its concentrations are usually not altered during dairy product processing.[57] However, the vitamin D contents of dairy product are considered low relative to other dietary sources, such as high-fat fish and bovine liver. Nevertheless, dairy-derived vitamin D is important because other sources are not regularly consumed by the populations of many countries, and other vitamin D sources may contain high levels of cholesterol.[58] Therefore, dairy products are the main dietary source of vitamin D in several countries and are commonly fortified with additional vitamin D.[58,59] In the United States, the maximum limits of vitamin D supplementation are approximately 100 IU/milk serving or 40-80 IU/yogurt serving.[58] Therefore, the consumption of the three recommended servings of dairy every day provides at most 300 IU of vitamin D, which is less than the current recommendation of 600 to 800 IU/day. This deficit should be satisfied by other dietary sources.

Although the DRI recommendations for calcium and vitamin D intake only considered the benefits for bone health, consuming ≥ 3 dairy portions every day, as recommended by the DG, also protects against T2DM and IRS.[11-14,18-21,23,24,26,36] Thus, a dairy intake that meets the DG might provide benefits with respect to T2DM, provided that appropriate vitamin D levels are maintained by means of other dietary sources or adequate solar exposure.[58]

According to the International Dairy Federation, the worldwide current estimated average consumption of dairy seems to be far from the recommendations.[60] This estimate is based on total milk production and not in its actual intake, which can lead to small variations in the values. The average *per capita* consumption of milk in 2009 was 103 L, corresponding to approximately 280 mL per day. Although in 2009 there was an increase of 8% in the estimated consumption compared to consumption in 2000, this amount is far below the recommended dietary allowances of at least three servings a day. It should also be considered that this consumption is not equally distributed among the different territories around the world.[56,61]

Conclusions

The results of the epidemiological studies indicate that the consumption of at least 3 servings of low-fat dairy products as part of a healthy diet is crucial to reduce the risk of developing T2DM. There are few

intervention studies that explored the effects of dairy or its components (calcium or vitamin D) on T2DM development and treatment. In some of them high doses of calcium and/or vitamin D were tested. Nevertheless, the majority of the analyzed intervention studies reported that the consumption of calcium and vitamin D may be beneficial in preventing and treating T2DM. Although this topic needs further investigation, the consumption of low-fat dairy consumption may be an important strategy to prevent and control T2DM, especially because of the low estimate values of dairy consumption by people from different parts of the world.

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