SPECIAL REVIEW

THE RS7903146 SNP OF TCF7L2 GENE AND ITS ASSOCIATION WITH THE METABOLIC SYNDROME

a review

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Abstract

Objective: To Conduct a systematic review of the literature in order to clarify and discuss the effects of SNP rs7903146 in the TCF7L2 gene and predisposition to Metabolic Syndrome (MS) modulation by dietary factors such variant. Methods: We performed a review of the literature in a systematic way from original studies between 2000 and 2013, found in Medline, PubMed, Wiley library, SciELO, ScienceDirect, Springer link, The University of Adelaide, DeepDyve, Cambridge journals. Results: The clinical trials reported in this study indicated a significant correlation between the risk allele of rs7903146 polymorphism and pathophysiological characteristics of MS, with the most consistent findings with changes in glucose homeostasis, insulin metabolism and atherogenic dyslipidemia for each study population. Conclusions: This review highlights the scientific evidence for rs7903146 polymorphism as one of the etiologic basis for MS. However, demonstrates the need for greater standardization of investigations, to reduce possible population variables with potential influence on the results, such as environmental factors and genetic heterogeneity.

Keywords: Metabolic Syndrome; TCF7L2; Single Nucleotide Polymorphism; Review.

INTRODUCTION

Of increasing prevalence, in addition to multiple etiologies and not fully explained, the Metabolic Syndrome (MS) is a complex disorder pointed as a result of the combination of several factors, such as overweight/obesity, sedentary lifestyle and poor eating habits.

The MS leads to an increase in cardiovascular risk, clinically identified by significant increases in blood pressure, fasting blood glucose levels, measures of waist circumference and serum concentrations of triglycerides (TG), which may be accompanied by a reduction in the levels of high-density lipoproteins (HDL).[1] It is a global epidemic, affecting a quarter of the adult population worldwide. Previous evidences[1,2] suggest that some people are genetically predisposed to metabolic disorders characteristic of MS, being generated from the interaction between excessive feeding, physical inactivity and genetic factors.

The genetic predisposition of MS is polygenic character, being credited to a series of genetic variants. Recent advances in studies of the human genome have enabled the identification of several genes associated with this syndrome. Many of genetic variants identified so far are characterized as Single Nucleotide Polymorphisms (SNP), which represent distinct changes in the sequence human genome responsible for triggering of various physiological disorders.[1,2,3] Different from the most classic mutations, the SNPs present a higher frequency in the population (higher than the 1%) and originate from a point mutation, representing the change of a nitrogen base in the DNA sequence.[1]

The identification of polymorphisms that influence the MS is a major focus of research for better understanding of the mechanisms underlying its pathogenesis.[3,4,5] In this case, common changes in gene Transcription Factor 7-Like 2 (TCF7L2) have recently been associated with such pathophysiological condition, with results that are consistently played in different populations.[4,1] A SNP in this gene in particular, rs7903146, is characterized by an exchange, in position 299 of the gene, a thymine (T) by a cytosine (C).[6] The gene TCF7L2, located on chromosome 10, is responsible for encoding the transcription factor TCF7L2.[1]

The process of heterodimerization of TCF7L2 with β-cateninas form, at the nucleus, a complex activator of expression of other genes,[5] including those responsible for encoding Glucagon-Like Peptide 1 (GLP-1) by L intestinal cells, in addition to insulin and proteins involved in the exocytosis of granules of this hormone in the pancreas.[4] In pancreatic β-cells, this transcription factor will be intermediate in signaling induced by GLP-1, responsible for stimulation of proliferation, neogenesis and development of these cells.[5] Other functions attributed to this transcription factor are normal development of the pancreas and its islets during embryonic growth, differentiation of adipocytes and adipogenesis.[7,13]

Understanding the genetic basis of MS can provide a vision of new metabolic pathways that identify potential therapeutic targets and intervention mechanisms. Thus, the present study aims to review recent experimental studies on physiological effects of single nucleotide polymorphisms, specifically the polymorphism rs7903146 in TCF7L2 gene and its role in the predisposition of Metabolic Syndrome. In addition, another focus of the study was to analyze the results of studies that have evaluated promising gene-nutrient interactions modulating the effect of this polymorphism.

METHODS

It was done a systematic review of the literature with original studies, researched in the databases: Medline, PubMed, Wiley library, SciELO, ScienceDirect, Springer link, The University of Adelaide, Deepdyve, Cambridge Journals using the following descriptors: metabolic syndrome, TCF7L2, SNP, gene-diet interaction. The articles were pre-selected from the abstracts information available in Portuguese and English languages and published in the period between 2000 and 2014.

Inclusion criteria were: clinical studies, preferably with controlled and randomized approach, studying the correlation between the polymorphism rs7903146 in TCF7L2 gene and comorbidities associated with Metabolic Syndrome, it was also an inclusion criteria the demonstration that genotypes were in Hardy-Weinberg equilibrium, to exclude possible genotypic errors.

RESULTS AND DISCUSSION

ALLELIC AND GENOTYPE FREQUENCIES

Initially, we evaluated the frequency of genotypes and alleles among the studies included. All the analyzed articles indicate that the genotypes (CC, CT and TT) were consistent with Hardy-Weinberg equilibrium and showed distinct frequencies among different populations.[3,5,18] It was shown that, in the Brazilian population, the risk allele (T) frequency varies between 5 and 37%, with lower frequency among individuals of Japanese descent.[18] In fact, the genetic heterogeneity of the Brazilian population is perhaps a factor of

great influence on the study of this polymorphism association with diseases. In a previous study among Brazilians[3,6] with Type 2 Diabetes Mellitus, a higher incidence of risk allele (T) was shown among diabetic individuals when compared to those without diabetes. Between Europeans, the T allele frequency varied from 36.4 to 46.3%.[4,9,10,17]

Phillips et al. found a higher number of individuals carrying genotypes with the risk allele among individuals with MS when compared to healthy controls.[4] However, few studies have evaluated the frequency of this polymorphism among individuals with MS. In general, the authors investigated diverse ethnic groups and possible inconsistencies in results may reflect differences in sample size, gender and genetic heterogeneity. The main differences between the studies are linked to the frequencies of the alleles of risk and environmental factors that are specific to each population studied and may influence its effect on disease. Table 1 summarizes the frequency of the risk allele and genotype among different studies.

Table 1 - Genotype and allele frequencies for rs7903146 polymorphism among Europeans and Brazilians

Reference	Subjects	Genotype and Allelic frequencies	Reference	Subjects	Genotype and Allelic frequencies
Europeans			Brazilians		
Delgado-Lista *et al.*	n = 450 (35-70 years) (Ireland, UK, Norway, France, Netherland, Spain, Polone e Sweden) BMI: 20-40 kg/m·	HW Eq **CC:** 55.7% **CT:** 37.9% **TT:** 6.4%	Silva,	n = 198 families Triunfo/PE	**Diabetics:** CC: 42.2% CT: 46.8% (**T allele:** 34%) TT: 11% **Non-diabetics:** CC: 47.7% CT: 43.5% (**T allele:** 30.6%) TT: 8.8%
Schafer *et al.*	n = 1110 non-diabetic germans	HW Eq **T Allele:** 30% **CC:** 49.1% **CT:** 42.7% **TT:** 8.2%	Barra *et al.*	n = 252 Brazilians Brasília/DF > 40 years; Type2 DM: 113 Non-diabetics: 139	**T Allelle in Type2DM:** 35.8% **T Allele in controls:** 27% Total sample T Allele: 30.9%
Corella *et al.*	n = 7018 spainards (2993 Males; 4025 Females) Type2 DM With cardiovascular risk factors	HW Eq **CC:** 39.5% **TT:** 14.2% **CT:** 46.3%	Dutra *et al.*	n = 104 Healthy Brazilans Randon selected Brasilia/DF	HW Eq **C Allele:** 63% **T Allele:** 37% **CC:** 41.34% **CT:** 43.27% **TT:** 15.39%
Phillips *et al.*	n= 1754 europeans Female: 35-60 years Male: 45-60 years **Cases:** MS **Controls:** Non-MS (NCEP ATP III)	HW Eq **CC:** 45% **CT:** 44% **TT:** 11%	Franco *et al.*	n = 222 Japanise descendant Brazilians Normal Oral Glucose Tolerance Test (OGTT) Median Age: 56.2 years	HW Eq **T Allele:** 5.5% **CC:** 89% **CT:** 11%

HW Eq: Hardy-Weinberg

SNP RS7903146 AND ANTHROPOMETRIC CHARACTERISTICS

Table 2 summarizes the main scientific findings of the anthropometric variations in individuals carrying the polymorphism rs7903146. The case-control study developed by Phillips and collaborators showed that European individuals carrying the T allele, when compared with individuals homozygous CC (or non-carriers) present higher values of body mass index (BMI) and waist circumference, so that the risk genotype was more frequent among individuals with MS.[4]

Such results are confronted with those presented by other studies that investigating the populations of eight European countries and did not find a significant association between this genetic variant and BMI, weight or body fat.[17] Among the non-carriers of the risk allele, there it was reported a greater muscle mass, stature or body water percentage.[17] In the adult Germans, association between the risk allele (population frequency of T allele was 30%) and BMI values were not detected.[9] Similar frequency (27.2%) was reported to Danishes, but this variant was not associated with anthropometric variables in that population.[1]

Of all studies presented here, the work developed by Saadi et al. (2008) was the only one who reported significant association between the T allele and reduced values of waist circumference,[11] but they do not provide a casual explanation to this association and also discuss that this finding could be take with care because the small sample size. A possible explanation to this association could lie in the fact that the population studied is formed by pre-diabetic or diabetic patients that have weight loss secondary to a compensation for the glucose metabolism disturbance. Glucose intolerance and its increased energy demand could consume fat reserves and promote reductions of circumference measurements.

Considering possible variations of outcome between genders, Phillips et al. studies the association of the polymorphism and anthropometric profile in male and female individuals and found that among females carrying the referred variant it was shown increased abdominal obesity and BMI, both characteristics of the MS.[4] Although the effect has followed the same trend in male subjects it did not reach statistical significance in this gender. The waist circumference is the anthropometric measurement more strongly correlated with the diagnosis of MS,[1] however it was not presented evidence for the association of the rs7903146 polymorphism with waist circumference. Only the results of Phillips et al. showed a higher waist circumference (WC) among those patients with MS and carrying this variant.[4]

Table 2 - The rs7903146 polymorphism and antropometric parameters

(continued)

Reference	Subjects	Study type	Analysed Variables	Results
Phillips *et al.*	n = 1754 Females: 35-60 years Males: 45-60 years **Cases:** MS **Controles:** Healthy subjects	Case-control	BMI and Waist Circunference MS (NCEP ATP III)	**T allele carryers:** ▲ BMI Waist Circunference BF
Delgado-Lista *et al.*	n = 450 (35-70 years) (Ireland, UK, Norway, France, Netherland, Spain, Polone e Sweden) BMI: 20-40 kg/m·	Transversal	Electrical Bioimpedance MS (NCEP AT III)	**CC homozygous:** ▲ Slim mass* Heigth* Body water* Without defferences on BMI

Table 2 - The rs7903146 polymorphism and antropometric parameters

(conclusion)

Reference	Subjects	Study type	Analysed Variables	Results
Warodomwichit *et al.*	n =1083 Europeans Age: 17-92 years	Case-control	Height, Weight, Waist Circunference, BMI	Without significant associations
Saadi *et al.*	n = 368 Arab Emirates Normanl Glucose: 188 Pre-diabetics: 85 Type 2DM: 95		Height, Weight, Waist Circunference, BMI	**TT Genotype** Waist Circunference* ↓ BMI without associations

*(p·0.05) . IDF = *International Diabetes Federation; BF*: body fat; *NCEP*: *National Cholesterol Education Program*

SNP RS7903146, CLINICAL AND BIOCHEMICAL ANALYSIS

The majority of the studies analyzed showed strong association between the variant rs7903146 and reduced secretion and/or sensitivity of insulin, with model of recessive inheritance (TT) showing greater association with such variables. Measures of HOMA-β were used to assess the ability of pancreatic cells to release insulin, while HOMA-IR has been shown to be the main parameter used to measure the insulin action in peripheral organs. A few studies have examined the pattern of secretion and/or sensitivity of insulin among persons with MS carrying the variant rs7903146.

Tables 3 and 4 summarize the main effect of this polymorphism on biochemical parameters, such as HOMA-β, HOMA-IR, incretins, glucose, and plasma lipids. All articles here evaluated report close relationship between the rs7903146 variant and disturbances in the production and/or secretion of insulin, indicating greater susceptibility to the development of Type 2 Diabetes Mellitus (T2DM). Second Saadi et al. reported that 78% of individuals with MS also presented T2DM showing a strong correlation between these disorders. In addition, studies show a significant association between the presence of risk allele and increased insulin resistance as measured by HOMA-IR.[4,15] However, these studies did not investigate the physiological homeostasis after oral tolerance test (OGTT) or intravenous tolerance test (IVGTT) to glucose. Indeed, the association of the risk allele (T) with the insulin resistance is not well explained. A hypothesis proposed by Damcott and collaborators suggests that the variation in the TCF7L2 gene may be associated with dysfunction in adipocytes and a consequent deposition of triglycerides in peripheral tissues resulting in insulin resistance.[1] Authors such as Delgado-Lista et al., Schafer et al., Warodomwichit et al. and Saadi et al. associated the rs7903146 polymorphism with decreased insulin secretory capacity of pancreatic cells. However, such hypothesis does not allow effective conclusion, since conflicting results have been found in experiments conducted in different populations.

Habener and collaborators showed that the cellular signaling triggered by GLP-1 is crucial for the development and proliferation of pancreatic β-cells, therefore, the changes in the release of insulin by the pancreas may be the result of a defect in entero--insular axis, responsible for production and signalling of incretins, but not by a reduction of cell mass in the pancreas. This was reinforced by Schafer et al. that reported that individuals carrying the risk allele showed no difference in insulin secretion during application of intravenous glucose as compared to those not carrying this variant.

The differences in the release of insulin between the two groups, carriers and non-carriers of the T allele, were detected only when glucose was administered during the oral tolerance test (OGTT), indicating a possible influence of the variant in TCF7L2 gene on the production of insulin induced by incretins. In order to exclude possible influence of this polymorphism in TCF7L2 gene on the pancreatic cell mass, the authors tested individuals with oral arginine and concluded

that insulin secretion induced by this amino acid was not significantly affected by the presence of the allele T. These findings reported show that the rs7903146 variant was not associated with changes in basal levels of GLP-1 or its secretion during the OGT test, suggesting that a decrease in sensitivity to GLP-1 signals, but not its decreased synthesis, seems to be the etiological basis of insulin disorder secondary to the variant in the TCF7L2 gene.

In short, despite the role of TCF7L2 in regulating the production of GLP-1, plasma concentrations of this incretin during OGT test were not significantly influenced by the rs7903146 polymorphism. Thus, the lowest response of insulin mediated by GLP-1 seems to be the result of decreased responsiveness of pancreatic β-cells instead of a reduction in its secretion or insulin resistance. These results suggest that the variant in the TCF7L2 gene could increase the risk of physiological disturbance by a reduced secretion of insulin, rather than a decreased action of this hormone.[14,9]

With regard to changes in blood lipids, Warodomwichit et al. reported an association of the allele risk (T) with atherogenic dyslipidemia, increasing the levels of very low density lipoprotein (VLDL).[7] Individuals carrying the CC genotype showed lower risk of developing metabolic syndrome by presenting decreased triglycerides (TG) levels when compared to individuals carrying the allele T.

Only two of the previously published papers evaluated the effects of this genetic variation on the blood pressure. While Phillips et al. found a significant association between this polymorphism (T allele) and higher systolic and diastolic blood pressures, Delgado-Lista et al. found the contrary.[4,17]

Table 3 - Clinical and Biochemical Analysis and the rs7903146 Polymorphism

(continued)

Reference	Subjects	Study type	Analysed Variables	Results
Warodomwichit, D. *et al.*	n= 1083 healthy Europeans (515 Male and 568 Female) Age: 17-92 years	Coort 2 years	Glucose Insulin HOMA-IR HOMA-B	**CT +TT genotypes:** ↑ Fasting glucose* ↓ Fasting HOMA-B* ↑ [VLDL]* ↓ [LDL]* Trend to ↑ [TG] *
Saad*i et al.*	n = 368 subjects from Arab Emirates Normal glucose: 188 pre-diabetes: 85 Type 2DM: 95	Transversal Population based.	HOMA-IR HOMA-B Disease Stage: Normal glucose Pre-diabetes Diabetes MF (IDF) Systolic and Diastolic blood pressure	**MS prevalence:** Normal glucose: 19.3% Pre-diabetes: 46.4% Type2DM: 78.5% Without association between T allele and MS and its components

Table 3 - Clinical and Biochemical Analysis and the rs7903146 Polymorphism

(conclusion)

Reference	Subjects	Study type	Analysed Variables	Results
Barra *et al*	n = 252 Brazilians > 40 years; Type 2DM: 113 Non-diabetics: 139	Case-control	Clinical and Biochemical parameters	Association between TT homozygosity and Type2DM*
Corella, D. *et al.*	7018 Spainards (2993 Males; 4025 Females) Type2DM + cardiovascular risk factors	Randon sampling	Fasting Glucose, Total cholesterol, TG, HDL-c and LDL-c	**TT Genotype**: ↑ Type2DM - Association between genotypes and fasting glucose* - Without association between genotypes and lipids
Phillips CM *et al.*	n = 1754 Females: 35-60 years Males: 45-60 years **Cases: MS** **Controls:** Healthy males and females	Case-control	Fasting Glucose, TG HDL-c Total Cholesterol Insulin C Peptid HOMA-IR	**Females (CT/TT):** ↑ MS* ↑ HOMA-IR* ↑ [insulin] ↑ Systolic Blood Pressure* **Females CC:** ↑ Intake of Poli-insaturated fat acids

*(p·0.05).

IDF: *International Diabetes Federation.*

Table 4 - Clinical and Biochemical Analysis and the rs7903146 Polymorphism

(continued)

Reference	Subjects	Study type	Intervention	Results
Delgado-Lista . *et al.*	n = 450 (35-70 years) (Ireland, UK, Norway, France, Netherland, Spain, Polone e Sweden) BMI: 20-40 kg/m·	Transversal	[insulin] [glucose] HOMA-IR HOMA-B IVGTT (IS, AIRG, DI) Total Cholesterol TG HDL-c NEFA PAI-1	**CC homozygous:** (as compared to CT and TT genotypes) ↑ Systolic and Diastolica blood presure* Without associations with SI, DI, HOMA-B [glucose], [insulin] fasting **During IVGTT:** ↓ AIRG, DI e HOMA-B*
Schafer AS *et al.*	n = 1110 non-diabetic Germans	Case-control	GLP-1 release OGTT IVGTT; hyperglicemic clamp+ GLP-1 + arginine.	**CT and TT genotypes:** ↓ Insulin release ↑ Insulin sensitivity in a OGTT; **After IVGTT:** ↓ Insulin release induced by GLP-1

Table 4 - Clinical and Biochemical Analysis and the rs7903146 Polymorphism

(conclusion)

Reference	Subjects	Study type	Intervention	Results
Franco L.F. *et al.*	n = 222 Japanese derived Brazilians (M: 72; F: 150) Normal OGTT Age: 40 – 79 years	Prospective Population based	OGTT HOMA-IR HOMA-B Insulin Pro-insulin	Without association between T allele and Glucose intolerance **After OGTT:** T allele carryers have ↓ [insulin]* After 2hs OGTT
Calanna S. *et al.*	139 subjects BMI > 25kg/m· Fasting Glucose < 100mg/dL MS (n=29) Non-MS (n=67) (NCEP ATP III)		[glucose] [insulin] [C peptid] [glucagon] [GL-1] Plasmatic Lipids	**Baseline (SM):** ↓ HDL* ↑ TG* Fasting glucose* HOMA-IR* Total cholesterol* **(SM) after OGTT:** ↑ AUC Glucose (0-120)* AUC insulin (0-120)* AUC GIP (0-120) AUC GLP-1 did not differ between SM and Non-SM **(SM) after IVGTT:** ↑ AUC Glucose (0-10)* AUC insulin (0-60)*

*(p · 0.05). **Insulin release marks** [**AIRG =** acute insulin response to glucose; **DI =** disposition índex (IS X AIRG)]; IS: insulin sensitivity; NEFA: Non esterified fat acids; AUC: area under the curve; PAI-1: plasminogen inhibitor - 1.

GENE-NUTRIENTS INTERACTIONS

Results of a recent study add evidence that individuals with variants in TCF7L2 gene become more prone to atherogenic dyslipidemia, as well as have more difficulty of reduction of body fat when submitted to diets with nutritional specific compositions.(7) It is already known the differential secretion of incretins, mainly GLP-1, in response to the composition of fat and carbohydrates in the diet. As suggested by Grau et al., this diet stimulus and the decreased activity of GLP-1 caused by rs7903146 variant can result in different responses suggesting an interaction between variants in the TCF7L2 gene and macronutrient composition of the diet.(8) Regarding the stimulation of GLP-1 release by dietary fat, the adverse effect of the rs7903146 polymorphism is more pronounced when individuals with the risk allele have an excessive intake of this nutrient.(8,4)

As suggested by Grau et al., the increasing concentration of endogenous GLP-1 reduces the mobilization of fatty acids (FA) during fasting and or in response to satiety signs.[8] Therefore, genetic variants in the TCF7L2 gene could change individual response to restrictive diets for weight loss, depending on the composition of macronutrients in the diet. This is suggested by their experimental study, when individuals TT homozygous to the TCF7L2 polymorphism submitted to diets rich in fat had significantly smaller weight loss, smaller reduction of waist circumference and lower decrease in body fat mass.[8]

A study among individuals of European origin reported that carriers of the T allele for rs7903146 polymorphism as compared to non carriers presented a higher risk to the development of MS, mainly due to the presence of hypertriglyceridemia during

postprandial period, even having similar caloric and fat consumption.[7] The type of fat ingested also seems to exert direct influence on the development of MS. The intake of saturated fat (SFA) in particular, has proved to be an important modulator factor to the risk conferred by rs7903146 variant. According to the results of Phillips et al., the high intake of SFA by individuals carrying the T allele exacerbates the genetic susceptibility to MS.[4] Interesting, the increase in SM risk conferred by high SFA intake, was significantly higher among women with the genotype risk. High SFA consumption (above, approximately, 15% of the total dietary energy value) results in decreased sensitivity and increased resistance to insulin and high level of this hormone in carriers and non-carriers of T allele for rs7903146 polymorphism. Nonetheless, there is a significant exacerbation of this effect in the presence of T variant. Whereas ingestion of SFA is less than 15% of total dietary energy values, the insulin levels and its sensitivity do not differ between the TCF7L2 genotypes. In other words, there is a negative modulation due to the high consumption of saturated fat in the presence of this genetic variant, which is not observed in individuals without this variant and in those who have small SFA consumption.

As showed in Table 5 and 6, the majority of scientific reports assess the modulation of the effect of rs7903146 polymorphism by dietary fats. Considering the effects of the consumption of integral carbohydrates, Fisher et al. have identified a negative association between the consumption of such carbohydrate and occurrence of T2DM in subjects that did not have the rs7903146 variant.[14] However, in a cohort study the same authors demonstrated that patients carrying the T allele significantly reduced such beneficial effects on diabetes risk, providing evidence that this genetic variant negatively modulates the effects due to the consumption of integral carbohydrates.

Table 5 - Association between the rs7903146 polymorphism and dietetic factors

(continued)

Reference	Subjects	Study type	Intervention	Results
Warodomwichit, D. *et al.*	n = 1083 healthy Europeans (515 M e 568 F) Age: 17-92 years	Case-control	Diet with 700 kcal/m· Meal: 3% de PTN 14% de CHO 83% de LIP 240mg cholesterol poliinsaturated:saturated fat = 0.06	**Baseline (T allele carryers):** ↓ [LDL] and HOMA-B * ↑ [Glucose],[VLDL] and [TG]* ↑ MS risk * **TT Genotype + AGPI intake above mediane¥:** ↑ Fasting [VLDL]* ↑ [TG], quilomicrons* ↑ [VLDL] post-prandial* **CT and TT genotypes + High consumption (n-6):** ↑ [VLDL]* **High consumption (n-3) :** ↓ [VLDL] in CC, CT e TT ↓ (non significant for CT and TT genotypes)* Without associations between the T allele and MIFA, SFA, Total fat over fasting and post-prandial lipids

Table 5 - Association between the rs7903146 polymorphism and dietetic factors

(continued)

Reference	Subjects	Study type	Intervention	Results
Corella *et al.*	7018 Spainards (2993M; 4025 F) Type2 DM + cardiovascular risk factors	Randon sampling	Lipidic profile Cardiovascular events after MedDiet	Mean adherence to MedDiets: Score= 9 (0-14) **Low adherence to MedDiet (TT homozygous):** ↑ Fasting [glucose]* ↑ [Total Cholesterol], [LDL-c] e [TG]* Without association with HDL-c **High adherence to MedDiet (TT genotype; M and F):** Without association with fasting glucose and lipids During 4.8 years 262 cardiovascular events occurs (stroke, miocardial infarction and cardiovascular deaths) **TT genotype + low adherence:** ↑ Stroke risk + **trend** to be associated with total cardiovascular events **TT genotype + high adherence:** None association with cardiovascular events **TT genotype among controls:** ↑ Stroke risk CT genotype with intermediate risk
Phillips CM *et al.*	n= 1754 F: 35-60 years M: 45-60 years **Cases:** M and F with MS **Controls:** without MS (NCEP ATP III)	Case-control	24hs feeding recordatory each 2 moths (6 per year)	SFA intake modulates MS risk* **High SFA intake" + T allele:** ↑ MS risk* ↑ HOMA-IR and [insulin] **Low SFA intake:** Without any change on insulin related phenotypes.
Delgado-Lista	n = 450 (35-70 years) (Ireland, UK, Norway, France, Netherland, Spain, Polone e Sweden) BMI: 20-40 kg/m·	Transversal	[insulin] [glucose] HOMA-IR HOMA-B IVGTT (IS, AIRG, DI) Cholesterol TG HDL-c NEFA PAI-1	**CC genotype + High SFA intake':** ↑ IL-6 **TT genotype + High SFA intake:** ↓ IL-6 **TT genotype + Low SFA intake:** ↓ IL-6

*(p·0.05); *(· 7.36% of TEV); PTN: proteins; CHO: carbohidrates; LIP: lipids; PIFA: Poli-insatured fat acids; (n-3): omega-3; (n-6): omega-6; MIFA: monoinsatured fat acids; SFA: saturated fat acids; MedDiet: Mediterrain Diet.

Table 5 - Association between the rs7903146 polymorphism and dietetic factors

(conclusion)

Reference	Subjects	Study type	Intervention	Results
GRAU, K *et al*	771 obese Europeans F:579; M:192 BMI>30kgm· Age: 20-50 years	Randon sampling, multi-center (Sweden, Dinmark, Uk, Netherland, Tchec Republic, France and Spain) 10 weeks	Hipocaloric Diets [DEN - 600cal with low (20-25%) or high (40-45%) fat]	**TT genotype + Low fat Diet:** Higher decrease (3.3cm) in Waist Circunference the High fat diet* Higher decrease (2.4cm) in Waist Circunference than CT and CC genotypes. **TT genotype + High fat Diet:** ↓ HOMA-IR in 1.33 units*

*(p·0.05); #(·15.5% of TEV). DEN: Daily Energetic Needs (Resting Metabolic Rate x 1.3)

CONCLUSION

The analysis of the current experimental data suggests a strong association between the rs7903146 TCF7L2 gene variant and disorders in the metabolism of carbohydrates and insulin dysfunctions. Clinical evaluations allow us to infer that the polymorphism, a single nucleotide polymorphism in the TCF7L2 gene, promotes significant reduction in the synthesis and / or secretion of insulin by pancreatic β-cells. Possibly, the etiology of these dysfunctions is related to a reduced signalling of incretins in these cells, which confirms the role of the transcription factor TCF7L2 in the expression of cellular receptors for GLP-1 and GIP.

Despite the precarious nature of experimental evaluations in the context of metabolic syndrome, several studies show that the presence of this genetic variant, in association with dietary factors, mainly saturated fatty acids, increases the susceptibility to the development of disorders characteristics of this syndrome, such as insulin resistance and atherogenic dyslipidemia. However, little evidence of association between this variant with waist circumference or blood pressure was reported.

Although knowledge of the genetic etiological basis of Metabolic Syndrome is a promising aspect for the development of potential therapeutic strategies and preventive measures, there is much yet to understand before such information be translated into benefits in clinical practice. With respect to the nutritional aspects, although the main focus is the metabolism of carbohydrates and lipids, it is possible to study other implications of this polymorphism in clinical studies, correlating it with other nutritional disorders and dietary interventions. Despite the strong association between rs7903146 in TCF7L2 gene and metabolic disturbances, such variant role on Metabolic Synddrome is not clear. In general, there are discrepancies between many publications, so that inconsistencies in results may reflect differences in the criteria used for the definition of Metabolic Syndrome, the size of the population studied, gender differences, genetic heterogeneity or even the environmental factors that differ between populations studied.

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