Beta cell functionality and hepatic insulin resistance are major contributors to type 2 diabetes remission and starting pharmacological therapy: from CORDIOPREV randomized controlled trial

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In order to assess whether previous hepatic IR (Hepatic-$IR_{fasting}$) and beta-cell functionality could modulate type 2 diabetes remission and the need for starting glucose-lowering treatment, newly-diagnosed type 2 diabetes participants who had never received glucose-lowering treatment (190 out of 1002) from the CORonary Diet Intervention with Olive oil and cardiovascular PREVention study (a prospective, randomized and controlled clinical trial), were randomized to consume a Mediterranean or a low-fat diet. Type 2 diabetes remission was defined according to the American Diabetes Association recommendation for levels of HbA1c, fasting plasma glucose and 2h plasma glucose after oral glucose tolerance test, and having maintained them for at least 2 consecutive years. Patients were classified according to the median of Hepatic-$IR_{fasting}$ and beta-cell functionality, measured as the disposition index (DI) at baseline. Cox proportional hazards regression determined the potential for Hepatic-$IR_{fasting}$ and DI indexes as predictors of diabetes remission and the probability of starting pharmacological treatment after a 5-year follow-up. Low-Hepatic-$IR_{fasting}$ or high-DI patients had a higher probability of diabetes remission than high-Hepatic-$IR_{fasting}$ or low-DI subjects (HR:1.79; 95% CI 1.06−3.05; and HR:2.66; 95% CI 1.60−4.43, respectively) after a dietary intervention with no pharmacological treatment and no weight loss. The combination of low-Hepatic-$IR_{fasting}$ and high-DI presented the highest probability of remission (HR:4.63; 95% CI 2.00−10.70). Among patients maintaining diabetes, those with high-Hepatic-$IR_{fasting}$ and low-DI showed the highest risk of starting glucose-lowering

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therapy (HR:3.24;95% CI 1.50−7.02). Newly-diagnosed type 2 diabetes patients with better beta-cell functionality and lower Hepatic-IR$_{fasting}$ had a higher probability of type 2 diabetes remission in a dietary intervention without pharmacological treatment or weight loss, whereas among patients not achieving remission, those with worse beta-cell functionality and higher Hepatic-IR$_{fasting}$ index had the highest risk of starting glucose-lowering treatment after 5 years of follow-up. (Translational Research 2021; 238:12−24)

Abbreviations: Adipo-IR = Adipose tissue insulin resistance index; ALT = alanine aminotransferase; AUC = area under curve; BMI = body mass index; CHD = coronary heart disease; CORDIOPREV = CORonary Diet Intervention with Olive oil and cardiovascular PREVention; DBP = diastolic blood pressure; DI = disposition index; FFA = free fatty acids; HDL-c = high-density lipoprotein; Hepatic-IR$_{fasting}$ = hepatic insulin resistance index derived from fasting values; IGI = insulinogenic index; ISI = insulin sensitivity index; IR = insulin resistance; LDL-c = low-density lipoprotein; LF diet = low-fat diet; Med diet = Mediterranean diet; MISI = muscular insulin sensitivity index; MUFA = monounsaturated fatty acids; OGTT = oral glucose tolerance test; PUFA = polyunsaturated fatty acids; SBP = systolic blood pressure; T2DM = type 2 diabetes mellitus; TG = triglycerides

At A Glance Commentary

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Background

Our current knowledge regarding the etiology of type 2 diabetes points to hepatic insulin resistance and beta cell functionality as two 2 major abnormalities underlying the disease. Previous studies have associated type 2 diabetes remission with weight loss, together with a decrease in liver fat content and a higher beta cell recovery.

Translational Significance

Patients with lower hepatic insulin resistance and better beta cell functionality had a higher probability of remission without significant weight loss or pharmacological treatment. These results suggest that clinicians could identify patients with specific phenotypes in early-diagnosed type 2 diabetes that could be the key to achieve higher remission rates without weight loss or pharmacological treatment.

INTRODUCTION

The prevalence of type 2 diabetes mellitus is steadily increasing worldwide with the resulting greater socioeconomic burden on health services, the economy and society.[1,2] When diabetes is presented as a comorbidity along with coronary heart disease (CHD), there is a greater risk of vascular complications.[3,4] The prevention of type 2 diabetes should therefore be a high priority in cardiovascular patients.

Two major pathophysiologic abnormalities are known to underlie most cases of type 2 diabetes: liver insulin resistance (IR) and defects in pancreatic beta cell function,[5-7] acting in a cyclical way, which has been expanded into what was subsequently termed the twin cycle hypothesis.[8,9] An excess of fat accumulation in the liver induces liver IR, causing rises in fasting plasma glucose and triggering an increase in insulin production. As a consequence, this phenomenon leads to impaired pancreatic beta cell function that results in the development of type 2 diabetes.[10]

It has recently been demonstrated that type 2 diabetes is reversible in patients who undergo bariatric surgery for obesity[11-13] and follow moderate energy restriction diets,[14] counteracting the fat accumulation in the liver and pancreas. However, the molecular mechanisms responsible for the remission are unclear. Some investigators have examined the involvement of IR and beta cell functionality status at the beginning of the disease,[15,16] For instance, Wang et al demonstrated that the status of these parameters before intense insulin treatment was key for long-term remission.[17] However, to the best of our knowledge, no long-term comparisons of different dietary patterns in individuals with hepatic IR and/or beta-cell dysfunction without pharmacological treatment or weight loss have been reported in cases of type 2 diabetes remission in patients with CHD.

Thus, our objective was to evaluate whether the previous status of hepatic IR and beta cell functionality could modulate type 2 diabetes remission rates in newly-diagnosed type 2 diabetes in patients with CHD from the CORDIOPREV (CORonary Diet Intervention with Olive oil and cardiovascular PREVention) study after dietary intervention without pharmacological treatment. In addition, considering the group of patients who failed to achieve remission, we aimed to

identify which group of these patients had more probability of starting glucose-lowering treatment, according to hepatic IR and beta cell function phenotypes.

MATERIALS AND METHODS

Study subjects. The current work was conducted within the framework of the CORDIOPREV study (Clinicaltrials.gov NTC00924937), an ongoing prospective, randomized, open, controlled trial including 1002 patients with CHD, who had their last coronary event more than 6 months before their enrolment in 2 different dietary models for 7 years, in addition to following the conventional treatment for coronary heart disease.[18] The participants were randomized to receive 2 diets: a Mediterranean (Med) diet or a low-fat (LF) diet. The inclusion and exclusion criteria have been reported previously.[18]

Patients who had diabetes diagnosed at the beginning of the study and were not receiving glucose-lowering treatment were included in the CORDIOPREV-DIRECT study (190 out of 1002 patients). The diabetes diagnosis was carried out according to the American Diabetes Association diagnosis criteria.[19] Of these, 7 patients could not be included due to their inability to perform the diagnostic test used in this work. Thus, the remaining 183 type 2 diabetes patients were distributed at baseline into 2 groups, according to the median of their hepatic insulin resistance index derived from fasting values (Hepatic-$IR_{fasting}$): 89 patients who had Hepatic-$IR_{fasting}$ values below the median (Low Hepatic-$IR_{fasting}$ group) and 93 patients who had Hepatic-$IR_{fasting}$ values above the median (High Hepatic-$IR_{fasting}$ group). One patient could not be classified because we were unable to obtain reliable Hepatic-$IR_{fasting}$ data for them at baseline.

The second classification of our population was carried out according to the median of the beta cell functionality values, measured as the disposition index (DI) at baseline. Of the 183 patients, 89 presented disposition index values above the median (High DI group), 90 showed disposition index values below the median (Low DI group) and 4 patients could not be classified due to technical difficulties in acquiring the baseline DI data.

The biochemical and laboratory measurements were performed as previously described.[20,21] All the patients gave written, informed consent to participate in the study. The trial protocol and amendments were approved by the local ethics committee of Reina Sofia University Hospital in Cordoba, following the Helsinki declaration and good clinical practices.

Randomization and masking. The procedure of randomization has been reported elsewhere.[18] Briefly, the randomization was based on the following variables: sex (male, female), age (under and over 60 years old) and previous myocardial infarction (yes, no). With this distribution, 8 different groups were created, with all the possible combinations of the above factors, to which the diets were assigned (block randomization). The dietitians were the only members of the intervention team to be aware of the dietary group of each participant.

Criteria for diabetes remission. Type 2 diabetes remission was defined as HbA1c <6.5%, fasting plasma glucose <126 mg/dL and 2 hours plasma glucose after 75 gr oral glucose tolerance test (OGTT) <200 mg/dL, and maintaining these levels for at least 2 consecutive years without the use of diabetes medication to lower blood glucose levels. The patients were tested yearly from the first year of follow-up and classified as remission or maintaining diabetes at fifth year of the study. In our population, 73 patients reverted from type 2 diabetes after 5 years of dietary intervention, while 110 participants had not achieved remission by the end of the follow-up period.

Glucose-lowering treatment. We also evaluated the patients who started glucose-lowering treatment during the follow-up period. Pharmacological treatment was prescribed by the primary care physicians or any other specialist who was not linked to the CORDIOPREV study, according to the standardized recommendations given by the international guidelines.[22] None of the CORDIOPREV study researchers were involved in the decision to start glucose-lowering treatment in those patients.

Study design and dietary assessment. The participants were randomized to receive 2 diets: a Med diet or a LF diet. The LF diet consisted of <30% total fat (<10% saturated fat, 12%−14% monounsaturated fat (MUFA), and 6%−8% polyunsaturated fat (PUFA), 15% protein, and a minimum of 55% carbohydrates. The Med diet comprised a minimum of 35% of calories as fat (22% MUFA fat, 6% PUFA fat, and <10% saturated fat), 15% proteins, and a maximum of 50% carbohydrates.[18] In both diets, the cholesterol content was adjusted to <300 mg/d.

The dietary assessment has been described recently.[23] Participants in both intervention groups received the same intensive dietary counseling. Nutritionists carried out individual interviews at baseline and every 6 months, and quarterly group education sessions were held with up to 20 participants per session and separate sessions for each group.

Estimation of insulin resistance and beta cell function indexes. The patients underwent a standard OGTT analyzed by the Matsuda and DeFronzo method[24] every year during the follow-up period. After an overnight fast, blood was sampled from a vein before oral

glucose intake (0 min) and again after a 75 g flavored glucose load (Trutol 75; Custom Laboratories, Baltimore, MD, USA). Blood samples were taken at 30, 60, 90 and 120 min to determine glucose and insulin concentrations.[24] Since C-peptide was not measured, the insulin data might be confounded by clearance. The following indexes were calculated at baseline and every year during the follow-up period. The hepatic insulin resistance index derived from fasting values (Hepatic-$IR_{fasting}$) was calculated as fasting insulin (pmol/l) × fasting glucose (mmol/l), since, as suggested by Abdul-Ghani et al,[25] hepatic glucose production (HGP) is the primary determinant of the FPG concentration,[26] and FPI concentration is the primary regulator of HGP,[27] the product of FPG and FPI primarily reflects hepatic insulin resistance.[25] The muscle insulin sensitivity index (MISI) was measured according to the Abdul-Ghani et al method[21]: MISI = (dG/dt)/mean plasma insulin concentration, where dG/dt is the rate of decay of plasma glucose concentration from its peak value to its nadir during the OGTT. Other IR indices determined were: insulin sensitivity index (ISI) = $10{,}000/\sqrt{}$ ([fasting insulin (pmol/l) × fasting glucose (mmol/l)] × [mean OGTT insulin (pmol/l)] × [mean OGTT glucose (mmol/l)])[24]; and HOMA-IR.[28] Insulin secretion was measured by the insulinogenic index (IGI): IGI = (30 min insulin−fasting insulin [pmol/l])/(30 min glucose−fasting glucose [mmol/l]).[29] Finally, beta cell function was estimated by calculating the disposition index (DI) as follows: DI = ISI × [AUC30 min insulin/AUC30 min glucose], where AUC30 min is the area under the curve between baseline and 30 min of the OGTT for insulin (pmol/l) and glucose (mmol/l) measurements, respectively, calculated by the trapezoidal method.[30] The adipose tissue insulin resistance index (Adipo-IR) was calculated as the product of fasting free fatty acids (FFA) x fasting plasma insulin.[31]

Statistical analyses. SPSS statistical software (IBM SPSS Statistics version 21.0) was used for statistical analysis of the data. The normal distribution of variables was assessed using the Kolmogorov-Smirnov test. The data are represented as the mean ± SEM for continuous variables and as frequencies for categorical variables. P values ≤ 0.05 were considered statistically significant. The statistical differences in the metabolic variables between groups were evaluated by 1-way ANOVA. Qualitative variables were compared using the Chi-square test. We used the total AUC of the different postprandial parameters following the trapezoid rule to assess the magnitude of change during the postprandial state, as in a previous study carried out by our group.[32] A repeated-measures ANOVA test was used to determine the statistical differences between variables at baseline and during the follow-up period. The post hoc statistical analysis was completed using Bonferroni's multiple comparison tests. For the statistical analysis we used age, sex, BMI, fasting glucose, use of statins, family history of diabetes, ethnicity, HDL-cholesterol, and triglycerides as covariables.

Previous further analysis, we classified our patients as above/below the median in each of the diabetes indexes calculated (ISI, DI, Hepatic-$IR_{fasting}$, IGI, MISI, Adipo-IR and HOMA-IR) and performed a logistic regression analysis in order to identify the potential influencers in diabetes remission. The model outcomes showed that only DI and Hepatic-$IR_{fasting}$ were associated with the probability of diabetes remission (Supplemental Table 1). We sought for the relevance of including BMI or weight change as a confounding variable in the Cox models and we found no statistical significance for weight change in our outcomes but did for BMI, so we decided to include it in our analysis. According to that, a Cox proportional hazards model was applied to identify the potential association of Hepatic-$IR_{fasting}$, DI and its combination with the time of type 2 diabetes remission and with the probability of initiating glucose-lowering treatment. In order to adjust these associations, the full model was implemented, with the following variables: sex, age, BMI, triglycerides, HDL-c, treatment (according to dose) with statins, family history of diabetes, and diet consumed during the intervention. Since fasting glucose was included in calculation formula for DI and Hepatic-$IR_{fasting}$, it was excluded from the Cox model in order to avoid overestimations.

RESULTS

Baseline characteristic of the participants according to hepatic insulin resistance and beta-cell functionality phenotypes. The characteristics of the subjects according to the hepatic insulin resistance phenotype (High versus Low) at baseline are shown in Table I. We observed that the High Hepatic-$IR_{fasting}$ group had higher values of BMI, waist circumference, diastolic blood pressure (DBP), glucose, glucose 2h-OGTT, insulin, HOMA-IR, triglycerides, alanine aminotransferase (ALT), Hepatic-$IR_{fasting}$ and Adipo-IR than the Low Hepatic-$IR_{fasting}$ group at baseline (all, $P < 0.05$). Moreover, subjects with High Hepatic-$IR_{fasting}$ had a lower age ($P= 0.001$) and ISI ($P< 0.001$) compared with the Low Hepatic-$IR_{fasting}$ group.

The characteristics of the subjects according to the beta cell functionality phenotype at baseline are shown in Table II. We found that the High DI group had lower values of glucose, glucose 2h-OGTT, HOMA-IR and

Table I. Baseline characteristics of participants according to hepatic insulin resistance phenotype

n	Low hepatic-$IR_{fasting}$ 89	High hepatic-$IR_{fasting}$ 93	*P-value*
Men/Women (n)	74/15	78/15	0.895
Age (years)	62.2 ± 1.0	57.7 ± 0.9	0.001
BMI (Kg/m^2)	29.6 ± 0.4	32.6 ± 0.5	<0.001
Waist circumference (cm)	101 ± 0.9	110 ± 1.1	<0.001
SBP (mm Hg)	136 ± 2.1	138 ± 2.1	0.374
DBP (mm Hg)	74.8 ± 1.2	78.9 ± 1.2	0.017
HbA1c (%, mmol/mol)	6.58 ± 0.07, 48 ± 0.5	6.79 ± 0.09, 51 ± 0.6	0.072
Glucose (mg/dl)	104 ± 1.7	117 ± 3.0	<0.001
Glucose 2h-OGTT (mg/dl)	191 ± 7.5	218 ± 9.1	0.022
Insulin (mU/l)	7.10 ± 0.41	16.3 ± 1.3	<0.001
HOMA-IR	2.25 ± 0.08	6.28 ± 0.41	<0.001
HDL-cholesterol (mg/dl)	42.7 ± 1.0	40.5 ± 1.1	0.122
LDL-cholesterol (mg/dl)	92.2 ± 2.8	91.0 ± 2.7	0.760
Triglycerides (mg/dl)	131 ± 7.7	154 ± 7.2	0.031
C-reactive protein (mg/L)	2.97 ± 0.25	2.94 ± 0.22	0.934
Use of statins (%)	87.6%	87.1%	0.912
ALT (U/L)	25.8 ± 1.3	30.6 ± 1.4	0.012
ISI	3.69 ± 0.15	1.74 ± 0.08	<0.001
DI	0.57 ± 0.05	0.49 ± 0.03	0.140
Hepatic-$IR_{fasting}$	933 ± 30	2544 ± 166	<0.001
MISI	0.024 ± 0.032	0.018 ± 0.002	0.092
IGI	0.50 ± 0.05	0.87 ± 0.21	0.097
Adipo-IR	22.4 ± 1.5	50.2 ± 3.6	<0.001

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; ISI, insulin sensitivity index; DI, disposition index; Hepatic-$IR_{fasting}$, hepatic insulin resistance index derived from fasting values; MISI, Muscular insulin sensitivity index; IGI, insulinogenic index; ALT, alanine aminotransferase; OGTT, Oral Glucose Tolerance Test.
Values expressed as mean ± SEM. frequencies in men/women;
One-Way ANOVA *P*-values. $P < 0.05$ indicates significant differences between groups.

Hepatic-$IR_{fasting}$ than the Low DI group (all $P < 0.05$). In addition, subjects with a High DI phenotype had higher LDL-c, ISI, DI and IGI values compared with the Low DI group.

In addition, we analyzed the change in weight and BMI between baseline and after 5 years of intervention according to the Hepatic-$IR_{fasting}$ and DI groups (Supplemental Table 2). We did not observe any significant differences in weight and BMI change values between the groups after the intervention.

Probability of type 2 diabetes remission. We performed a Cox proportional hazards regression analysis to determine the probability of type 2 diabetes remission according to the hepatic insulin resistance phenotype after 5 years of intervention (Fig 1A). Compared to the High Hepatic-$IR_{fasting}$ patients (reference group), the Low Hepatic-$IR_{fasting}$ patients presented a 2.3-fold higher probability of type 2 diabetes remission (HR: 2.30; 95% CI: 1.41−3.73). After adjustment for all possible confounder variables mentioned in the statistical section in the methodology, the Cox model outcomes showed that that Low Hepatic-$IR_{fasting}$ patients presented a 1.8-fold higher probability of remission (HR: 1.79; 95% CI: 1.06−3.05). In addition, the model showed the association of baseline BMI, where each SD of lower BMI corresponded to a 1.07-fold higher probability of remission (HR: 1.07; 95% CI: 1.01−1.14).

Further, we performed a second Cox analysis to evaluate the probability of type 2 diabetes remission according to the beta cell functionality phenotype after 5 years of intervention (Fig 1B). The results showed that patients with higher DI values had 2.4 more probability of type 2 diabetes remission than patients with low DI values (reference group) (HR: 2.40; 95% CI: 1.46−3.95). After adjustment with the variables mentioned above, the Cox model outcomes showed that High DI patients presented a 2.7-fold higher probability of remission (HR: 2.66; 95% CI: 1.60-4.43). In addition, the model showed the association of baseline BMI, where each SD of lower BMI represented a 1.11-fold higher probability of remission (HR: 1.11; 95% CI: 1.05−1.18).

At this point, we wondered whether the patients' phenotype had the same effect in each diet on their probability of diabetes remission. Here, we found the same effect regardless of the diet, so these diets did not modulate diabetes remission differently in our study groups (Hepatic-$IR_{fasting}$ and DI groups) (Supplemental Table 3). In this regard, we also observed that there were no

Table II. Baseline characteristics of participants according to beta-cell functionality phenotype

N	Low DI 90	High DI 89	*P-value*
Men/Women (n)	78/12	72/17	0.295
Age (years)	59.3 ± 1.0	60.3 ± 1.0	0.469
BMI (Kg/m^2)	30.7 ± 0.4	31.6 ± 0.5	0.186
Waist circumference (cm)	105 ± 1.1	105 ± 1.2	0.909
SBP (mm Hg)	139 ± 2.3	135 ± 1.9	0.184
DBP (mm Hg)	78.2 ± 1.3	75.7 ± 1.1	0.148
HbA1c (%, mmol/mol)	6.79 ± 0.10, 51 ± 0.7	6.59 ± 0.07, 48 ± 0.5	0.105
Glucose (mg/dl)	122 ± 2.9	100 ± 1.4	<0.001
Glucose 2h-OGTT (mg/dl)	244 ± 8.1	165 ± 6.7	<0.001
Insulin (mU/l)	12.9 ± 1.3	10.8 ± 0.8	0.176
HOMA-IR	5.12 ± 0.47	3.57 ± 0.20	0.003
HDL-cholesterol (mg/dl)	41.4 ± 1.2	41.7 ± 0.9	0.828
LDL-cholesterol (mg/dl)	86.2 ± 2.9	96.6 ± 2.6	0.008
Triglycerides (mg/dl)	143 ± 7.4	144 ± 7.9	0.919
C-reactive protein (mg/L)	3.02 ± 0.24	2.83 ± 0.23	0.558
Use of statins (%)	90%	87.6%	0.616
ALT (U/L)	28.6 ± 1.3	27.8 ± 1.4	0.654
ISI	2.35 ± 0.14	2.99 ± 0.17	0.004
DI	0.30 ± 0.01	0.76 ± 0.05	<0.001
Hepatic-IR$_{fasting}$	2096 ± 189	1446 ± 81	0.002
MISI	0.023 ± 0.003	0.019 ± 0.002	0.393
IGI	0.36 ± 0.03	1.0 ± 0.2	0.004
Adipo-IR	39.4 ± 3.3	33.6 ± 3.0	0.200

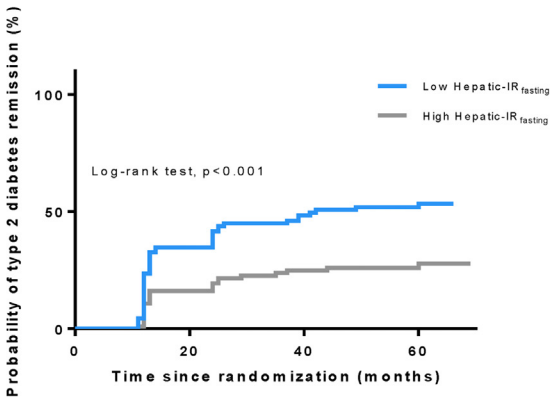
Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; ISI, insulin sensitivity index; DI, disposition index; Hepatic-IR$_{fasting}$, hepatic insulin resistance index derived from fasting values; MISI, Muscular insulin sensitivity index; IGI, insulinogenic index; ALT, alanine aminotransferase; OGTT, Oral Glucose Tolerance Test.
Values expressed as mean ± SEM. frequencies in men/women;
One-Way ANOVA *P*-values. $P < 0.05$ indicates significant differences between groups.

statistical differences in number of remission/non remission among the type of diet studied ($\chi 2$, $P = 0.741$).

Finally, to evaluate which index, DI or Hepatic-IR$_{fasting}$, had a better predictive effect on the probability of type 2 diabetes remission, we divided our patients into 4 groups, according to the DI and Hepatic-IR$_{fasting}$ values at baseline. Next, we performed a Cox regression analysis to determine the probability of type 2 diabetes remission according to these groups (Fig 1C). The results showed that patients with the highest values of DI and the lowest values of Hepatic-IR$_{fasting}$ presented a greater probability of type 2 diabetes remission than the High Hepatic-IR$_{fasting}$ & Low DI group (HR: 5.40; 95% CI 2.47−11.81). The Low Hepatic-IR$_{fasting}$ & Low DI and High Hepatic-IR$_{fasting}$ & High DI groups presented intermediate values for probability of type 2 diabetes remission (HR: 2.80; 95% CI 1.19−6.60 and HR: 2.93; 95% CI 1.27−6.79, respectively). However, after adjustment with the possible confounder variables, the Cox model outcomes showed that the group of patients with the highest values of DI and the lowest values of Hepatic-IR$_{fasting}$ presented a greater probability of type 2 diabetes remission than the High Hepatic-IR$_{fasting}$ & Low DI group (HR: 4.63; 95% CI 2.00−10.70). Furthermore, after adjustment, only the High Hepatic-IR$_{fasting}$ & High DI groups presented a higher probability of type 2 diabetes remission in comparison with the reference group (HR: 3.63; 95% CI 1.50−8.80). In addition, the model showed the association of baseline BMI, where each SD of lower BMI corresponded to a 1.09-fold higher probability of remission (HR: 1.09; 95% CI: 1.02−1.16).

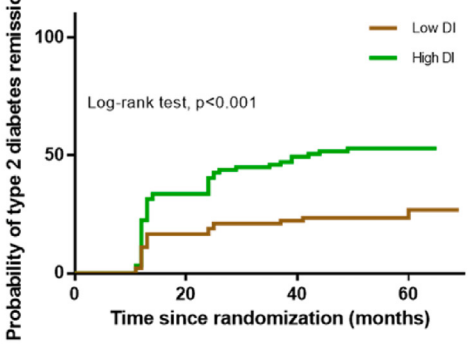
Probability of starting glucose-lowering treatment. We performed a COX proportional hazards regression analysis to determine the probability of starting type 2 diabetes glucose-lowering treatment according to the hepatic insulin resistance and beta cell functionality phenotypes during 5 years of follow-up (Fig 2). The results showed that patients with higher Hepatic-IR$_{fasting}$ values had a higher probability of starting type 2 diabetes pharmacological treatment (HR: 2.21; 95% CI: 1.34−3.65) than the low Hepatic-IR$_{fasting}$ group. Likewise, patients with lower DI values also had a greater probability of starting glucose-lowering treatment than those presenting higher DI values (HR: 1.98; 95% CI: 1.20−3.24). However, after adjustment with the possible confounder variables mentioned in the

A



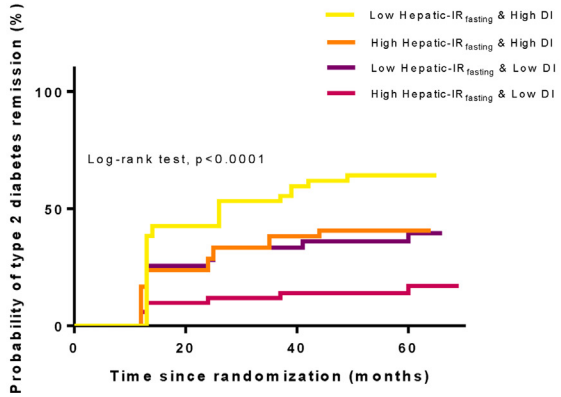
Hepatic-IR$_{fasting}$		HR	95% CI for HR	
			Lower	Upper
High Hepatic-IR$_{fasting}$ (ref.)		1.00	1.00	1.00
Low Hepatic-IR$_{fasting}$	*Unadjusted*	2.30	1.41	3.73
	*Adjusted**	1.79	1.06	3.05

B



DI		HR	95% CI for HR	
			Lower	Upper
Low DI (ref.)		1.00	1.00	1.00
High DI	*Unadjusted*	2.40	1.46	3.95
	*Adjusted**	2.66	1.60	4.43

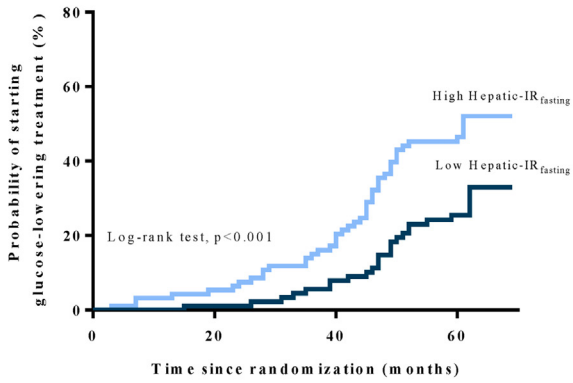
C



Hepatic-IR$_{fasting}$ & DI		HR	95% CI for HR	
			Lower	Upper
High Hepatic-IR$_{fasting}$ & Low DI (ref.)		1.00	1.00	1.00
Low Hepatic-IR$_{fasting}$ & Low DI	*Unadjusted*	2.80	1.19	6.60
	*Adjusted**	2.23	0.90	5.56
High Hepatic-IR$_{fasting}$ & High DI	*Unadjusted*	2.93	1.27	6.79
	*Adjusted**	3.63	1.50	8.80
Low Hepatic-IR$_{fasting}$ & High DI	*Unadjusted*	5.40	2.47	11.81
	*Adjusted**	4.63	2.00	10.70

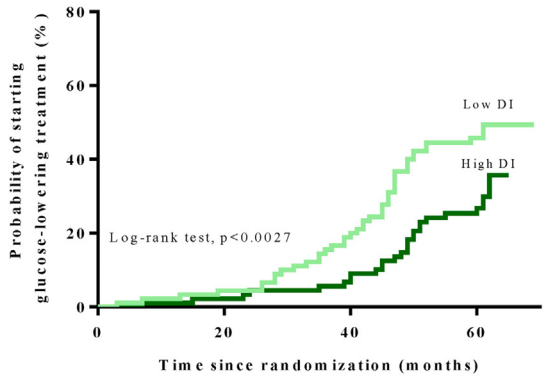
Fig 1. Probability of type 2 diabetes remission. Probability of type 2 diabetes remission according to hepatic insulin resistance index derived from fasting values (Hepatic-IR$_{fasting}$) (A), beta cell functionality measured as disposition index (DI) (B) and the combination of Hepatic-IR$_{fasting}$ and DI groups (C). The graphics represent the curves of probability without adjustment. These models were adjusted for age, sex, BMI, triglycerides, HDL-c, treatment with statins, family history of diabetes and diet consumed during the intervention. The HR between groups was calculated.

A



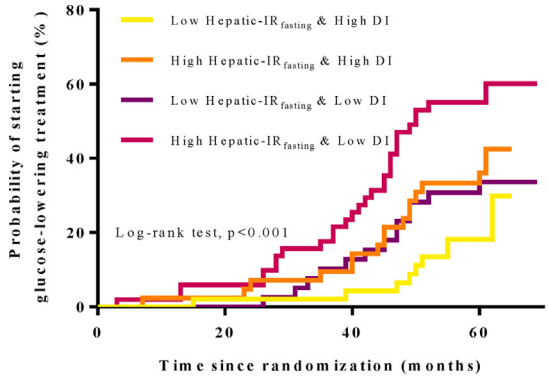
HIRI		HR	95% CI for HR	
			Lower	Upper
Low Hepatic-IRfasting (ref.)		1.00	1.00	1.00
High Hepatic-IRfasting	*Unadjusted*	2.21	1.34	3.65
	*Adjusted**	1.67	0.96	2.90

B



DI		HR	95% CI for HR	
			Lower	Upper
High DI (ref.)		1.00	1.00	1.00
Low DI	*Unadjusted*	1.98	1.20	3.24
	*Adjusted**	2.23	1.32	3.76

C



HIRI & DI		HR	95% CI for HR	
			Lower	Upper
Low Hepatic-IRfasting & High DI (ref.)		1.00	1.00	1.00
Low Hepatic-IRfasting & Low DI	*Unadjusted*	1.94	0.83	4.55
	*Adjusted**	1.93	0.81	4.57
High Hepatic-IRfasting & High DI	*Unadjusted*	2.20	0.97	4.99
	*Adjusted**	1.43	0.60	3.38
High Hepatic-IRfasting & Low DI	*Unadjusted*	4.07	1.93	8.61
	*Adjusted**	3.24	1.50	7.02

Fig 2. Probability of starting glucose-lowering treatment. Probability of starting treatment for type 2 diabetes according to hepatic insulin resistance index derived from fasting values (Hepatic-$IR_{fasting}$) (A), beta-cell functionality measured as disposition index (DI) (B) and the combination of Hepatic-$IR_{fasting}$ and DI groups (C). The graphics represent the curves of probability without adjustment. These models were adjusted for age, sex, BMI, triglycerides, HDL-c, treatment with statins, family history of diabetes and diet consumed during the intervention. The HR between groups was calculated.

statistical section, the COX model showed that having higher Hepatic-$IR_{fasting}$ values did not increase the probability of starting pharmacological treatment but did show a significant association for of baseline BMI values (HR: 1.07; 95% CI: 1.01−1.13) and family history of diabetes (HR: 1.66; 95% CI: 1.01−2.73) (Supplemental Table 5). Regarding DI groups, the COX model outcomes showed that after adjustment, those patients with lower DI values presented a 2.23-fold higher probability of starting treatment (HR: 2.23; 95% CI: 1.32−3.76). In addition, it also showed the association for baseline BMI values (HR: 1.11; 95% CI: 1.05−1.17) and family history of diabetes (HR: 1.66; 95% CI: 1.01−2.74) (Supplemental table 5).

At this point, we evaluated the likelihood of starting type 2 diabetes pharmacological treatment according to the diets consumed and hepatic insulin resistance and beta cell functionality phenotypes to find out whether the patients' phenotype had the same effect in each diet on their probability of starting treatment. We found that the same effect was produced regardless of the diet, so these diets did not modulate the likelihood of starting pharmacological treatment differently in our study groups (Supplemental Table 4).

When we evaluated the probability of starting pharmacological treatment in the population classified according to Hepatic-$IR_{fasting}$ and DI, we observed that patients with the highest values of Hepatic-$IR_{fasting}$ and the lowest values of DI presented a higher probability of starting glucose-lowering treatment than the Low Hepatic-$IR_{fasting}$ & High DI group (HR: 4.07; 95% CI: 1.93−8.61). The Low Hepatic-$IR_{fasting}$ & Low DI and High Hepatic-$IR_{fasting}$ & High DI groups did not present any differences in the probability of starting treatment compared to the Low Hepatic-$IR_{fasting}$ & High DI group used as a reference. The same was observed in the COX model after adjustment with the variables mentioned above, with the group of patients with High Hepatic-$IR_{fasting}$ & Low DI presenting a 3.24-fold higher probability of starting glucose-lowering treatment than the reference group (HR: 3.24; 95% CI: 1.50−7.02). In this case, the model also included the baseline BMI values (HR: 1.09; 95% CI: 1.02−1.16) which are associated with starting treatment (Supplemental table 5).

Beta cell function and insulin resistance. We evaluated the IR and beta cell function as assessed by the validated indexes during the follow-up period (Supplemental Fig. 1) and observed higher ISI and lower Hepatic-$IR_{fasting}$ in the Low Hepatic-$IR_{fasting}$ group than in the High Hepatic-$IR_{fasting}$ group throughout the study ($P<$ 0.001). However, we found no significant differences in the DI index between both groups.

When we compared the DI classification groups, the High DI group had higher DI values compared with patients with Low DI values. Regarding the Hepatic-$IR_{fasting}$ and ISI indexes, no significant differences were observed between the DI groups.

Levels of FFA, ALT and Adipo-IR index. We evaluated the FFA on the OGTT, carried out at baseline and after 5 years of follow-up (Supplemental Fig. 2). We observed higher FFA plasma levels in Low DI subjects ($P=$ 0.044) than in the High DI group. However, we detected no differences in FFA plasma levels between Hepatic-$IR_{fasting}$ groups.

Moreover, we evaluated the Adipo-IR and ALT levels at baseline and after 5 years of follow-up (Supplemental Fig. 2). We observed higher Adipo-IR and ALT levels in High Hepatic-$IR_{fasting}$ subjects ($P<$ 0.001 and $P=$ 0.017, respectively) than in the Low Hepatic-$IR_{fasting}$ group. After that, we evaluated these parameters in the DI groups, but found no differences in ALT levels or Adipo-IR index between the groups.

DISCUSSION

In this study, we found that patients with lower hepatic insulin resistance values at the beginning of the study had a higher probability of type 2 diabetes remission compared with those who had higher Hepatic-$IR_{fasting}$ values after a dietary intervention without weight loss or glucose-lowering treatment. Likewise, patients with better beta cell functionality presented higher type 2 diabetes remission rates than those who had lower DI values. Therefore, we found that those with a combination of lower Hepatic-$IR_{fasting}$ and higher DI values presented the highest probability of type 2 diabetes remission. Moreover, the group of patients with a combination of higher Hepatic-$IR_{fasting}$ and lower DI showed a higher probability of starting pharmacological treatment for type 2 diabetes after 5 years of intervention among those patients maintaining diabetes. Our results showed that previous status of both indexes are potential contributors to type 2 diabetes remission after a dietary intervention without weight loss or pharmacological treatment. However, only DI and its combination with Hepatic-$IR_{fasting}$ influenced the probability of starting glucose-lowering treatment in those patients who did not achieve diabetes remission.

Type 2 diabetes is a multifactorial disease whose development is dependent on environmental and genetic factors. Its pathophysiology is mainly characterized by an increase in insulin resistance and a loss of beta cell function.[33] Several authors have investigated

both mechanisms as a way of preventing or delaying this disease.[34,35] It is crucial to gain a better understanding of this problem, given the fact that type 2 diabetes is a global health problem whose prevalence is increasing dramatically[36]. In the last few decades, the efforts of the scientific community have also been directed towards the study of diabetes remission, which, despite the traditional doctrine, has been shown in recent years to be possible.[37-39] Most of the authors have associated type 2 diabetes remission with weight loss, together with a decrease in liver fat content and higher beta cell recovery.[9,39] However, to the best of our knowledge, these studies were based on the characteristics of the participants at the beginning of studies and remission was achieved after bariatric surgery, pharmacological treatment or dietary intervention with the aim of weight loss. Thus, in our study, we aimed to go further and identify whether different pathophysiological phenotypes (hepatic insulin resistance and beta cell functionality) might provide the basis for the development of an individualized tool to better predict type 2 diabetes remission in response to a healthy dietary treatment during 5 years of follow-up in which remission was achieved without any pharmacological treatment or weight loss.

Our study demonstrates that diabetic patients with lower Hepatic-$IR_{fasting}$ levels at baseline had a higher probability of type 2 diabetes remission than those who had higher values of Hepatic-$IR_{fasting}$. Even though a lower hepatic IR has already been established as a potential factor for promoting the remission of type 2 diabetes,[37,40] this effect has been associated to major weight loss with a possible diminishing in liver fat, or after pharmacological treatment. In our study, patients with higher Hepatic-$IR_{fasting}$ values at baseline did not experience type 2 diabetes remission, probably due to the lower insulin sensitivity and higher hepatic IR that they presented from the beginning of the study. According to the twin-cycle hypothesis,[9,12] fat accumulation in the liver could have triggered insulin resistance and initiated the cycle affecting the insulin production by the pancreas. Moreover, the higher hepatic IR levels found in the High Hepatic-$IR_{fasting}$ group, together with their higher level of ALT after 5 years of intervention, would suggest an increase in liver fat in those patients.[41] It has been demonstrated that increased liver fat levels are associated with hepatic IR, inadequate suppression of hepatic glucose production, and hence increased fasting plasma glucose.[14,42,43] Therefore, patients with High Hepatic-$IR_{fasting}$ seem to have a non-reversible metabolic dysfunction, since the dietary intervention did not succeed in improving either the IR or the adipose tissue metabolic dysfunction in those patients.

Beta cell damage in the early stages of type 2 diabetes can be restored to normal function through diet-induced weight loss, as has been previously demonstrated by the DiRECT trial.[37] In line with these results, the patients with better beta cell functionality at the beginning of our trial presented a higher probability of type 2 diabetes remission than those who had lower DI values. These subjects, in the Low DI group, presented lower LDL-c values at baseline, which have been associated with higher type 2 diabetes risk[44]; they also showed lower beta cell functionality values during the 5 years of follow-up than those with higher DI values, who probably still had a reversible metabolic status. According to the twin-cycle hypothesis proposed recently to explain the pathophysiology of diabetes, in addition to the higher DI values which increase the probability of remission, our results showed that even with small increases of probability (HR:1.1), compared to the HR of those with a higher DI (HR:2.7), those with lower BMI values also had a higher probability of remission, since these patients are expected to present less fat deposit in visceral organs such as the liver. Therefore, early intervention with healthy diets in subjects with better beta cell functionality at the beginning of the trial leads to a higher probability of achieving type 2 diabetes remission, without the use of pharmacological treatment or drastic weight loss. Our results are in agreement with a previous study showing that patients with a better pancreatic beta cell function before bariatric surgery had an increased chance of type 2 diabetes remission after the surgery.[16]

Further, to identify which phenotype had a better predictive value, we divided our population, taking into account both the hepatic insulin resistance and beta cell functionality indexes. We found that both indexes contribute equally to the remission of type 2 diabetes. In fact, it is the synergy of both phenotypes, lower Hepatic-$IR_{fasting}$ and higher DI values, which better predicts type 2 diabetes remission. These results suggest that hepatic IR and beta cell functionality are the physiological mechanisms which contribute most to the onset of type 2 diabetes. For this reason, identifying these phenotypes in early diagnosed diabetic patients could be the key to achieving higher type 2 diabetes remission rates. In our study, both dietary treatments (low-fat and Mediterranean diets) exerted similar effects on type 2 diabetes remission. The 2 diets studied have similarities in terms of the lack of caloric restriction and being considered healthy cardioprotective dietary patterns which are low in saturated fatty acids and high in fiber and high-complex carbohydrates. Similarly, it has been reported that dietary intervention in diabetic patients,

such as the consumption of a hypocaloric diet for 6 months, can lead to a recovery of beta cell function, a decrease in liver fat and a return of serum ALT to normal levels.[37,45]

On the other hand, there is little scientific literature available about the risk of starting glucose-lowering treatment in diabetic patients according to the level of the hepatic insulin resistance and beta cell functionality indexes. The only relevant study was published by Esposito et al,[46] reporting that a Mediterranean diet can delay the need for antihyperglycemic drug therapy in overweight patients with newly diagnosed type 2 diabetes. In our study, the dietary intervention led to a lower probability of starting glucose-lowering treatment only in High DI patients, due to their better glucose homeostasis control and in those with a combination of Low Hepatic-$IR_{fasting}$ and High DI values. In addition, our results suggest the involvement of genetic factors associated to the increased probability of starting pharmacological treatment, since those with a family history of diabetes presented more probability of initiating treatment.

The major strength of this study is that, to the best of our knowledge, this is the first approach to assess type 2 diabetes remission according to hepatic insulin resistance and beta cell functionality phenotypes after a dietary intervention with 2 healthy diets with no caloric restriction or weight loss and without any pharmacological treatment in patients with CVD, which is a relevant finding, since the progression of type 2 diabetes in these patients severely increases the risk of a new cardiovascular event.[47] However, certain limitations should be highlighted. First, this research is based on a long-term, well-controlled dietary intervention, which ensures the quality of the study, but may not reflect the level of compliance in a free-living population. The second limitation is that the prevention of type 2 diabetes was not the primary endpoint of the CORDIOPREV trial, although it was a secondary objective of this study. And finally, since C-peptide was not measured, insulin data might be confounded by clearance. However, there are no reasons to believe that the randomization would not have worked in such a large subset of participants, taking into account that the baseline characteristics in the current study were similar in the groups of patients analyzed in this study.

In conclusion, our study shows that newly-diagnosed type 2 diabetes and coronary heart disease patients with better beta cell functionality and lower hepatic insulin resistance values had a higher probability of type 2 diabetes remission. Moreover, among patients who remained diabetic, those with the worst beta cell functionality and higher hepatic insulin resistance had a higher risk of starting glucose-lowering treatment after 5 years of dietary intervention.

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Conflict of Interest: All the authors have read the journal's policy on conflicts of interest. None of the authors declare any conflict of interest. All the authors have read the journal's authorship agreement.

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Trial Registration

Clinicaltrials.gov NTC00924937. https://clinicaltrials.gov/ct2/show/NCT00924937

DATA AVAILABILITY

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.trsl.2021.07.001.

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