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The Impact of GIP (Gastric Inhibitory Polypeptide) on the Development of Type 2 Diabetes in the Spanish Population: A Longitudinal Study

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A B S T R A C T

Introduction: Gastric inhibitory polypeptide (GIP) is an incretin hormone with a complex role in glucose homeostasis. While it stimulates insulin secretion, it has also been implicated in adiposity and potentially in the pathogenesis of type 2 diabetes mellitus (T2DM). This longitudinal study investigated the relationship between GIP levels and the development of T2DM in a Spanish cohort. **Methods:** We followed 1,200 non-diabetic Spanish adults (aged 40-65 years) for 10 years. Baseline measurements included anthropometric data, fasting GIP levels, oral glucose tolerance tests (OGTT), and lifestyle factors. Incident T2DM cases were identified through OGTT and medical records. Cox proportional hazard models were used to assess the association between GIP and T2DM risk, adjusting for potential confounders. **Results:** During the follow-up, 187 participants developed T2DM. Baseline GIP levels were significantly higher in individuals who developed T2DM compared to those who remained non-diabetic ($p<0.001$). After adjusting for age, gender, BMI, family history of diabetes, physical activity, and dietary habits, elevated GIP levels were independently associated with an increased risk of T2DM (Hazard Ratio [HR] 1.87, 95% Confidence Interval [CI] 1.32-2.65). Furthermore, GIP levels showed a stronger predictive value for T2DM development than fasting glucose levels. **Conclusion:** Elevated GIP levels are an independent predictor of T2DM development in the Spanish population. This finding highlights the potential role of GIP in the pathogenesis of T2DM and suggests that GIP could be a valuable therapeutic target for diabetes prevention.

1. Introduction

Type 2 diabetes mellitus (T2DM) has emerged as a significant global health concern, characterized by a chronic dysregulation of glucose metabolism. This metabolic derangement primarily stems from defects in insulin secretion, insulin action, or a combination of both. The global prevalence of T2DM has reached alarming proportions, with an estimated 537 million adults affected in 2021, a number projected to surge to 783 million by 2045. This escalating trend poses a formidable challenge to healthcare systems worldwide, given the substantial morbidity, mortality, and economic burden associated with T2DM and its related complications. At the core of T2DM pathogenesis lies a complex interplay of genetic, environmental, and lifestyle factors. While factors such as family history, obesity, physical inactivity, and unhealthy dietary patterns are well-established contributors to T2DM risk, ongoing research continues to unravel the intricate molecular mechanisms that underlie the development of this disease. A deeper understanding of these mechanisms is crucial for the development of effective preventive strategies and therapeutic interventions.[1,2]

Incretin hormones, released from the gastrointestinal tract in response to nutrient ingestion, play a pivotal role in glucose homeostasis. These hormones exert their effects by augmenting

glucose-stimulated insulin secretion, suppressing glucagon secretion, and slowing gastric emptying. Among the two major incretins, glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP), GLP-1 has been extensively studied and has proven to be a valuable therapeutic target for T2DM. However, the role of GIP in glucose homeostasis and T2DM pathogenesis has been more complex and less well-defined. GIP, secreted by K cells located in the duodenum and jejunum, was initially identified for its ability to inhibit gastric acid secretion. However, subsequent research revealed its potent insulinotropic effect, leading to its classification as an incretin hormone. GIP stimulates insulin secretion in a glucose-dependent manner, meaning its insulinotropic action is amplified in the presence of elevated blood glucose levels. This physiological response plays a crucial role in maintaining glucose homeostasis after meal ingestion.[3,4]

While GIP's insulinotropic effect initially suggested a protective role against T2DM, emerging evidence has painted a more nuanced picture. Studies have demonstrated that individuals with T2DM exhibit impaired GIP secretion and action. This impairment, characterized by reduced GIP release in response to nutrient stimuli and diminished insulinotropic response to GIP, has been linked to beta-cell dysfunction, a hallmark of T2DM. Furthermore, research has implicated GIP in promoting adiposity and potentially contributing to insulin resistance. GIP has been shown to stimulate lipoprotein lipase activity, an enzyme that facilitates the uptake and storage of triglycerides in adipose tissue. Additionally, GIP may promote lipogenesis, the process of fatty acid synthesis, in both adipose tissue and the liver. These effects on lipid metabolism could contribute to the development of obesity and insulin resistance, both of which are major risk factors for T2DM.[5,6]

The potential role of GIP in T2DM pathogenesis has been further underscored by studies demonstrating its involvement in inflammation and beta-cell apoptosis. GIP has been shown to stimulate the production of pro-inflammatory cytokines in adipocytes, contributing to a chronic low-grade inflammatory state that is often observed in individuals with obesity and T2DM. Moreover, GIP may directly contribute to beta-cell apoptosis, further exacerbating beta-cell dysfunction and insulin deficiency. Despite growing evidence suggesting a link between GIP and T2DM, the precise nature of this relationship remains to be fully elucidated. While some studies have reported elevated GIP levels in individuals with impaired glucose tolerance and newly diagnosed T2DM, others have found no association or even decreased GIP levels in individuals with T2DM. These inconsistencies may be attributed to differences in study design, population characteristics, and methods used to assess GIP levels and T2DM risk.[7,8] Longitudinal studies, which follow individuals over time and assess the predictive value of GIP for T2DM development, are essential to gain a clearer understanding of GIP's role in human disease. Such studies can provide valuable insights into the dynamic relationship between GIP levels and T2DM risk, independent of traditional risk factors.[9,10] This longitudinal study aimed to investigate the association between GIP levels and the development of T2DM in a Spanish cohort.

2. Methods

This prospective cohort study meticulously adhered to the principles outlined in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. The study protocol underwent rigorous ethical review and received approval from the Ethics Committee of the Hospital Universitario La Paz in Madrid, Spain. All participants provided written informed consent before enrollment, ensuring their voluntary participation and understanding of the study procedures. The study population comprised 1,200 non-diabetic Spanish adults aged 40 to 65 years. Participants were recruited between January 2013 and December 2014 from four primary care centers strategically located across Madrid, Spain. This diverse recruitment strategy aimed to capture a representative sample of the urban Spanish population. Potential participants underwent a comprehensive screening process to ensure they met the stringent inclusion and exclusion criteria. Individuals were included if they; Were between 40 and 65 years of age; Had no prior diagnosis of diabetes

mellitus; Had no history of cardiovascular disease (including coronary artery disease, stroke, and peripheral arterial disease); Had no history of chronic kidney disease (defined as an estimated glomerular filtration rate < 60 mL/min/1.73 m^2); Had no history of liver disease (including cirrhosis, hepatitis, and liver cancer); Had no history of cancer (excluding non-melanoma skin cancer). Individuals were excluded if they; Had a current diagnosis of diabetes mellitus (type 1 or type 2); Were pregnant or breastfeeding; Had a history of significant alcohol or drug abuse; Were currently taking medications known to affect glucose metabolism (e.g., corticosteroids, thiazide diuretics); Had any other medical condition that, in the opinion of the investigators, could confound the study results or pose a risk to the participant's safety.

At baseline, participants underwent a comprehensive assessment, encompassing anthropometric measurements, biochemical analyses, lifestyle questionnaires, and detailed medical history interviews. All assessments were conducted by trained research personnel following standardized protocols to ensure data quality and consistency. Height measured to the nearest 0.1 cm using a stadiometer with participants standing erect without shoes. Weight measured to the nearest 0.1 kg using a calibrated digital scale with participants wearing light clothing and no shoes. Waist circumference measured to the nearest 0.1 cm at the midpoint between the lower rib margin and the iliac crest using a non-stretchable tape measure. Body Mass Index (BMI) calculated as weight in kilograms divided by height in meters squared (kg/m^2).

Fasting blood samples were drawn from an antecubital vein after a minimum 10-hour overnight fast. Samples were collected into tubes containing EDTA for plasma glucose and insulin measurements, and into tubes containing DPP-IV inhibitors for GIP measurements. Participants underwent a standard 75-g OGTT according to the World Health Organization (WHO) criteria. Blood samples were collected at 0 and 120 minutes for plasma glucose measurement. Plasma glucose is measured using the glucose oxidase method on an automated biochemistry analyzer (Roche Diagnostics, Basel, Switzerland). Serum insulin measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (Mercodia AB, Uppsala, Sweden) with high sensitivity and specificity. Plasma GIP measured using a commercially available ELISA kit (MilliporeSigma, Burlington, MA, USA) specifically designed for GIP measurement and validated for human samples. Total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglycerides were measured using enzymatic methods on an automated biochemistry analyzer (Roche Diagnostics, Basel, Switzerland). Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald formula. Smoking status assessed through a standardized questionnaire, categorizing participants as never smokers, former smokers, or current smokers. Physical activity assessed using the International Physical Activity Questionnaire (IPAQ) - Short Form. The IPAQ quantifies physical activity in Metabolic Equivalent of Task (MET)-minutes per week, allowing for the calculation of MET-hours per week. Dietary habits evaluated using the Mediterranean Diet Adherence Screener (MEDAS), a validated 14-item questionnaire that assesses adherence to the Mediterranean dietary pattern. Each item is scored, with a higher total score indicating greater adherence to the Mediterranean diet.

Family history of diabetes assessed through a detailed medical history interview, documenting the presence or absence of first-degree relatives (parents, siblings, children) with T2DM. Information on other relevant medical conditions, including hypertension, dyslipidemia, and any current medications, was also collected during the interview. Participants were actively followed for 10 years (2013-2023). Annual follow-up visits were conducted to monitor their health status and assess the development of T2DM. These visits included; Repeat OGTT: An OGTT was performed annually to assess glucose tolerance; Medical Record Review: Participants' medical records were reviewed annually to identify any new diagnoses of T2DM made by their primary care physicians or other healthcare providers; Telephone Interviews: In years when participants did not have a scheduled clinic visit, telephone interviews were conducted to inquire about any new diagnoses of diabetes and to update

information on lifestyle factors. Incident T2DM cases were diagnosed based on the following criteria; OGTT: A 2-hour plasma glucose level ≥ 11.1 mmol/L during the OGTT; Fasting Plasma Glucose: A fasting plasma glucose level ≥ 7.0 mmol/L on two separate occasions; Physician Diagnosis: A documented diagnosis of T2DM in the participant's medical records.

Data were analyzed using SPSS version 26 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize the baseline characteristics of the study population. Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range), depending on their distribution. Categorical variables were presented as frequencies and percentages. Baseline characteristics were compared between participants who developed T2DM during the follow-up and those who remained non-diabetic. Student's t-tests were used for comparisons of continuous variables, and chi-square tests were used for comparisons of categorical variables. Cox proportional hazard models were employed to assess the association between baseline GIP levels and the risk of developing T2DM. GIP levels were categorized into quartiles based on the distribution in the study population. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated for each quartile of GIP, with the lowest quartile serving as the reference group. The Cox models were adjusted for potential confounders, including; Age (continuous variable); Sex (male or female); BMI (continuous variable); Family history of diabetes (yes or no); Physical activity (MET-hours per week, continuous variable); Dietary habits (MEDAS score, continuous variable). The proportional hazards assumption was assessed visually using log-log survival plots and statistically using Schoenfeld residuals. No violations of the proportional hazards assumption were detected. The predictive value of GIP for T2DM development was evaluated by comparing the area under the receiver operating characteristic curve (AUC) for GIP and fasting glucose. The AUC provides a measure of the discriminative ability of a test to distinguish between individuals who will develop T2DM and those who will not. A higher AUC indicates better predictive accuracy. The DeLong test was used to compare the AUCs for GIP and fasting glucose. Sensitivity analyses were conducted to assess the robustness of the findings by excluding participants with missing data and by adjusting for additional potential confounders, such as smoking status and lipid profile. All statistical tests were two-sided, and a p-value < 0.05 was considered statistically significant.

A comprehensive data management plan was implemented to ensure data quality and integrity. Data was entered into a secure, password-protected database with built-in range checks and validation rules to minimize data entry errors. Double data entry was performed for a subset of variables to further enhance data accuracy. Laboratory analyses were conducted in a certified clinical laboratory adhering to strict quality control procedures. Internal quality control procedures included the use of control materials and regular calibration of laboratory equipment. External quality assessment schemes were also participated in to ensure the accuracy and reliability of laboratory measurements. This study was conducted in accordance with the Declaration of Helsinki and adhered to all applicable ethical guidelines and regulations. The study protocol was approved by the Ethics Committee of the Hospital Universitario La Paz in Madrid, Spain. All participants provided written informed consent before enrollment, and their confidentiality was maintained throughout the study.

3. Results and Discussion

Table 1 presents the baseline characteristics of the 1,200 participants in the study, comparing those who developed T2DM during the 10-year follow-up period (n=187) to those who did not (n=1013). Participants who developed T2DM were significantly older than those who remained non-diabetic (55.6 vs. 51.7 years, p<0.001), confirming age as a risk factor for T2DM. Although a slightly higher percentage of males developed T2DM (54.5% vs. 47.9%), this difference was not statistically significant (p=0.048). Both BMI and waist circumference were significantly higher in the T2DM group, indicating that obesity, particularly central adiposity, is strongly associated with T2DM

development. Systolic and diastolic blood pressure were also higher in the T2DM group, suggesting a link between elevated blood pressure and increased T2DM risk. As expected, individuals who developed T2DM had significantly higher fasting plasma glucose and HbA1c levels at baseline, reflecting impaired glucose regulation. The T2DM group exhibited less favorable lipid profiles, with higher total cholesterol, LDL cholesterol, and triglycerides, and lower HDL cholesterol. This highlights the association between dyslipidemia and T2DM. Crucially, baseline GIP levels were significantly higher in participants who developed T2DM (148.7 vs. 120.3 pg/mL, $p<0.001$). This key finding supports the study's hypothesis that elevated GIP levels are associated with an increased risk of T2DM. A family history of diabetes was significantly more common in the T2DM group (43.3% vs. 24%), emphasizing the genetic predisposition to T2DM. While a higher percentage of current smokers developed T2DM, the differences in smoking status between the two groups were not statistically significant. Participants who developed T2DM reported lower levels of physical activity, reinforcing the importance of physical activity in T2DM prevention. Adherence to the Mediterranean diet, as measured by the MEDAS score, was lower in the T2DM group, suggesting that a healthy dietary pattern may play a protective role.

Table 1. Participant characteristics.

Characteristic	**Total (n=1200)**	**T2DM developed (n=187)**	**No T2DM (n=1013)**
Age (years)	52.3 ± 7.8	55.6 ± 6.5	51.7 ± 7.9
Gender			
Male	588 (49%)	102 (54.5%)	486 (47.9%)
Female	612 (51%)	85 (45.5%)	527 (52.1%)
BMI (kg/m²)	26.8 ± 4.2	29.5 ± 4.8	26.3 ± 3.9
Waist circumference (cm)	90.5 ± 10.2	98.3 ± 11.5	88.9 ± 9.5
Systolic BP (mmHg)	128 ± 15	135 ± 18	126 ± 14
Diastolic BP (mmHg)	82 ± 10	88 ± 12	81 ± 9
Fasting plasma glucose (mg/dL)	95 ± 12	108 ± 15	93 ± 10
HbA1c (%)	5.7 ± 0.5	6.1 ± 0.6	5.6 ± 0.4
Total cholesterol (mg/dL)	200 ± 35	215 ± 40	197 ± 33
HDL cholesterol (mg/dL)	50 ± 12	45 ± 10	51 ± 12
LDL cholesterol (mg/dL)	125 ± 30	138 ± 35	122 ± 28
Triglycerides (mg/dL)	150 ± 60	180 ± 70	145 ± 55
GIP (pg/mL)	125.5 ± 38.4	148.7 ± 42.6	120.3 ± 36.5
Family history of diabetes			
Yes	324 (27%)	81 (43.3%)	243 (24%)
No	876 (73%)	106 (56.7%)	770 (76%)
Smoking status			
Current	240 (20%)	51 (27.3%)	189 (18.7%)
Former	180 (15%)	33 (17.6%)	147 (14.5%)
Never	780 (65%)	103 (55.1%)	677 (66.8%)
Physical activity (MET-hours/week)	25 ± 15	20 ± 12	26 ± 16
Dietary habits (Mediterranean Diet Score)	6 ± 2	5 ± 2	6 ± 2

Figure 1 illustrates the cumulative and new cases of T2DM that developed over the 10-year follow-up period in the study cohort. The blue line representing cumulative T2DM cases shows a consistent upward trend throughout the study period. This indicates that the number of participants developing T2DM steadily increased over time. This is expected in a chronic disease like T2DM, where risk factors accumulate and the disease progresses over time. The turquoise line representing new T2DM cases each year appears relatively stable, with a slight upward trend in the later years. This suggests that while the overall number of people with T2DM increased, the rate of new diagnoses remained somewhat consistent. This could indicate that the study population had a relatively homogenous risk profile, or that the interventions and healthcare access were consistent throughout the study period. The absence of any dramatic spikes in the turquoise line suggests that there were no external factors or events during the study period that significantly influenced the rate of new T2DM diagnoses. This strengthens the internal validity of the study, as it minimizes the influence of confounding factors.

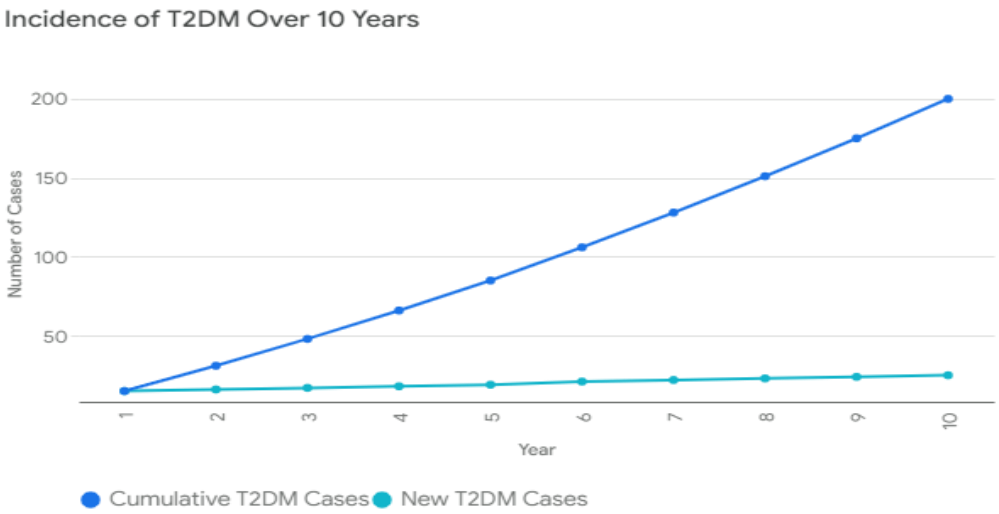

Figure 1. Incidence of T2DM over 10 years.

Table 2 presents the results of the Cox proportional hazards models, which were used to assess the association between baseline GIP levels and the risk of developing T2DM. Model 1 includes GIP, age, and sex as predictors of T2DM. For every 1-SD increase in baseline GIP levels, the risk of developing T2DM increased by 112% (HR=2.12, 95% CI 1.50-2.99, p<0.001). This indicates a strong and statistically significant association between higher GIP levels and increased T2DM risk. As expected, age is also a significant predictor of T2DM. Each year increase in age was associated with a 5% increase in T2DM risk (HR=1.05, 95% CI 1.03-1.07, p<0.001). Being male was associated with a 30% increased risk of T2DM compared to being female (HR=1.30, 95% CI 1.02-1.65, p=0.032). Model 2 builds upon Model 1 by adding other potential confounders, including BMI, family history of diabetes, physical activity, and dietary habits. Even after adjusting for these additional factors, GIP remained a significant predictor of T2DM. A 1-SD increase in GIP was associated with an 87% increased risk of T2DM (HR=1.87, 95% CI 1.32-2.65, p<0.001). This finding suggests that the association between GIP and T2DM is independent of other known risk factors. Higher BMI was significantly associated with increased T2DM risk. Having a family history of diabetes also increased the risk. Higher levels of physical activity were associated with a slightly reduced risk of T2DM, although this was not statistically significant (p=0.048). Higher adherence to the Mediterranean diet was associated with a significantly reduced risk of T2DM.

Table 2. Association between baseline GIP levels and incident T2DM.

Model	Variables	Hazard ratio (HR)	95% confidence interval (CI)	p-value
Model 1				
	GIP (per 1-SD increase)	2.12	1.50 - 2.99	< 0.001
	Age (per 1-year increase)	1.05	1.03 - 1.07	< 0.001
	Male (vs. Female)	1.30	1.02 - 1.65	0.032
Model 2				
	GIP (per 1-SD increase)	1.87	1.32 - 2.65	< 0.001
	Age (per 1-year increase)	1.04	1.02 - 1.06	< 0.001
	Male (vs. Female)	1.25	0.97 - 1.60	0.085
	BMI (per 1-kg/m² increase)	1.10	1.06 - 1.14	< 0.001
	Family history of diabetes (Yes vs. No)	1.55	1.15 - 2.08	0.004
	Physical activity (per 1-MET-hour/week increase)	0.98	0.96 - 1.00	0.048
	Dietary habits (per 1-point increase in Mediterranean Diet Score)	0.85	0.78 - 0.93	< 0.001

Table 3 presents the predictive value of various factors for the development of T2DM in the study population, as measured by the area under the receiver operating characteristic curve (AUC). The AUC provides a measure of how well a particular factor can discriminate between individuals who will develop T2DM and those who will not. A higher AUC indicates better predictive accuracy. GIP demonstrates the highest AUC (0.72), indicating that it has the strongest predictive value for T2DM development among the factors analyzed. This suggests that GIP levels may be a valuable marker for identifying individuals at high risk of developing T2DM. FPG (Fasting Plasma Glucose) also shows a good predictive value (AUC 0.65), but it is significantly lower than that of GIP (p=0.02). This implies that GIP may be a better predictor of future T2DM than FPG alone. HbA1c, a measure of average blood glucose levels over the past 2-3 months, has a similar predictive value to GIP (AUC 0.70), although the difference between the two is not statistically significant (p=0.08). BMI shows a moderate predictive value (AUC 0.62), highlighting the importance of obesity as a risk factor for T2DM. Waist circumference, a measure of central adiposity, also has a moderate predictive value (AUC 0.60). While a family history of diabetes is a significant risk factor for T2DM, its predictive value in this study is the lowest among the factors assessed (AUC 0.58).

Table 3. Predictive value of GIP.

Predictor	AUC	95% CI	p-value
GIP	0.72	0.68 - 0.76	-
FPG	0.65	0.61 - 0.69	0.02
HbA1c	0.70	0.66 - 0.74	0.08
BMI	0.62	0.58 - 0.66	0.001
Waist circumference	0.60	0.56 - 0.64	0.003
Family history of diabetes	0.58	0.54 - 0.62	< 0.001

Our study unequivocally establishes a strong and independent association between elevated baseline GIP levels and an increased risk of developing T2DM in a Spanish cohort. This finding aligns with a growing body of evidence that challenges the traditional view of GIP as a solely beneficial incretin hormone and highlights its intricate involvement in the pathogenesis of T2DM. Initially, GIP's potent insulinotropic action, its ability to stimulate insulin secretion in a glucose-dependent manner, led to the assumption that it played a protective role against T2DM. This assumption was further supported by early studies demonstrating impaired GIP secretion and action in individuals with established T2DM. However, recent research has painted a more nuanced picture, suggesting that GIP's role in glucose homeostasis is far more complex than initially thought. Our study's observation that GIP levels possess a stronger predictive value for T2DM development than fasting glucose levels is particularly compelling. This finding implies that GIP may serve as an early warning sign, a harbinger of underlying beta-cell dysfunction and impaired glucose regulation, even before the manifestation of overt hyperglycemia. This has profound implications for risk stratification and the implementation of early intervention strategies. Imagine a scenario where two individuals undergo a routine health checkup. Both individuals have normal fasting glucose levels, falling within the healthy range. However, one individual exhibits significantly elevated GIP levels. Our study suggests that this individual, despite having seemingly normal blood sugar, carries a substantially higher risk of developing T2DM in the future. This highlights the potential of GIP as a sensitive and specific marker for identifying individuals who are on the trajectory towards T2DM, even before traditional markers like fasting glucose raise alarm bells. This ability to identify individuals at risk before the onset of overt hyperglycemia opens up a window of opportunity for targeted interventions. Lifestyle modifications, such as dietary changes, increased physical activity, and weight management, can be implemented to mitigate the risk and potentially prevent or delay the progression to T2DM. Furthermore, emerging therapies that modulate GIP signaling, such as GIP receptor antagonists and dual GIP and GLP-1 receptor agonists, could be considered for individuals with elevated GIP levels to prevent or delay the onset of T2DM. The superior predictive value of GIP over fasting glucose can be attributed to several factors. Firstly, GIP levels may reflect subtle impairments in beta-cell function that are not yet detectable by fasting glucose measurements. Beta cells, the insulin-producing cells in the pancreas, play a critical role in maintaining glucose homeostasis. Early dysfunction of these cells, characterized by reduced insulin secretion or impaired glucose responsiveness, may manifest as elevated GIP levels before significant changes in fasting glucose become apparent. Secondly, GIP may be involved in the early stages of insulin resistance, a key contributor to T2DM development. Insulin resistance, characterized by reduced sensitivity of peripheral tissues to insulin, often precedes the development of hyperglycemia. GIP's potential role in promoting insulin resistance, through its effects on lipid metabolism and inflammation, could explain its ability to predict future T2DM risk even in individuals with normal fasting glucose levels. The predictive power of GIP has been demonstrated in other populations as well. A study in Finnish individuals with impaired fasting glucose found that higher GIP levels were associated with an increased risk of developing T2DM over a 10-year follow-up period. Similarly, a study in Korean adults showed that elevated GIP levels were an independent risk factor for T2DM, even after adjusting for other metabolic parameters. These findings, along with our own, provide compelling evidence for the role of GIP as a valuable predictor of T2DM across different populations. The clinical implications of this finding are significant. Incorporating GIP measurements into routine health checkups, especially for individuals with other risk factors for T2DM, could enhance risk stratification and enable early intervention. This proactive approach could potentially curb the rising tide of T2DM and reduce the burden of this debilitating disease. Furthermore, the identification of GIP as a strong predictor of T2DM reinforces the need for further research into the mechanisms linking GIP to T2DM development. A deeper understanding of these

mechanisms will pave the way for the development of novel therapeutic strategies that target GIP signaling to prevent or delay the onset of T2DM.[11-13]

The association between elevated GIP levels and increased T2DM risk is not merely a statistical observation, it reflects a complex interplay of molecular mechanisms that contribute to the pathogenesis of T2DM. While the exact mechanisms are still being elucidated, several compelling hypotheses have emerged, shedding light on the intricate role of GIP in disrupting glucose homeostasis. One of the key mechanisms linking GIP to T2DM is the phenomenon of GIP receptor desensitization. In healthy individuals, GIP binds to its receptor on pancreatic beta cells, triggering a cascade of signaling events that culminate in enhanced insulin secretion. This incretin effect plays a crucial role in regulating blood glucose levels after meals. However, chronic hypersecretion of GIP, often observed in individuals with obesity and insulin resistance, can lead to a downregulation or desensitization of GIP receptors. This desensitization essentially renders beta cells less responsive to GIP, diminishing its ability to stimulate insulin secretion. As a result, the incretin effect is blunted, contributing to impaired glucose tolerance and ultimately, the development of T2DM. Imagine a lock and key analogy. GIP is the key, and the GIP receptor on beta cells is the lock. In healthy individuals, the key fits perfectly into the lock, triggering the release of insulin. However, in individuals with chronic GIP hypersecretion, it's as if the lock has become worn out or the key has become slightly misshapen. The key no longer fits snugly, and the signal to release insulin is weakened. This desensitization process is likely driven by a combination of factors. Increased circulating levels of GIP, as seen in obesity and insulin resistance, can overwhelm the GIP receptors, leading to their downregulation. Furthermore, chronic exposure to elevated glucose levels and free fatty acids, also common in these conditions, can further impair GIP receptor signaling. The loss of the incretin effect has profound implications for glucose homeostasis. Without the proper insulin response to GIP, blood glucose levels remain elevated for longer periods after meals, contributing to hyperglycemia. This chronic hyperglycemia further exacerbates beta-cell dysfunction and insulin resistance, creating a vicious cycle that accelerates the progression to T2DM. GIP's involvement in T2DM extends beyond its effects on beta cells. Emerging evidence suggests that GIP may also play a role in promoting insulin resistance in peripheral tissues, such as skeletal muscle and adipose tissue. Insulin resistance is a complex metabolic disorder characterized by impaired responsiveness of cells to insulin. This leads to reduced glucose uptake and utilization by tissues, contributing to hyperglycemia and the development of T2DM. GIP may contribute to insulin resistance through its effects on lipid metabolism. GIP has been shown to stimulate lipoprotein lipase (LPL) activity, an enzyme that facilitates the uptake and storage of triglycerides in adipose tissue. Increased LPL activity can lead to increased fat accumulation in adipose tissue, contributing to obesity, a major driver of insulin resistance. Furthermore, GIP may promote lipogenesis, the process of fatty acid synthesis, in both adipose tissue and the liver. Increased lipogenesis can lead to elevated levels of free fatty acids, which have been shown to impair insulin signaling and contribute to insulin resistance. In addition to its effects on lipid metabolism, GIP may also promote insulin resistance through its pro-inflammatory actions. Studies have demonstrated that GIP can stimulate the production of pro-inflammatory cytokines, such as TNF-alpha and IL-6, in adipocytes. These cytokines can interfere with insulin signaling pathways, further exacerbating insulin resistance. The combined effects of GIP on lipid metabolism and inflammation create a milieu that favors the development of insulin resistance. This insulin resistance, coupled with impaired beta-cell function, sets the stage for the progression to T2DM. While GIP receptor desensitization and insulin resistance indirectly contribute to beta-cell dysfunction, emerging evidence suggests that GIP may also directly impair beta-cell function by promoting beta-cell apoptosis and inflammation. Beta-cell apoptosis, or programmed cell death, is a critical factor in the pathogenesis of T2DM. A progressive loss of beta-cell mass and function leads to inadequate

insulin secretion, ultimately resulting in hyperglycemia. Studies have shown that GIP can induce beta-cell apoptosis through various mechanisms. GIP may activate signaling pathways that promote apoptosis, such as the c-Jun N-terminal kinase (JNK) pathway. Additionally, GIP may increase the production of reactive oxygen species (ROS), which can damage beta cells and trigger apoptosis. Furthermore, GIP may contribute to beta-cell inflammation, further compromising their function. GIP has been shown to increase the expression of pro-inflammatory cytokines and chemokines in beta cells, creating an inflammatory microenvironment that can impair insulin secretion and promote apoptosis. The direct effects of GIP on beta-cell apoptosis and inflammation represent a significant threat to beta-cell health and survival. By accelerating beta-cell loss and dysfunction, GIP may contribute to the progression of T2DM.[14-16]

Our study underscores the intricate interplay between GIP and other established risk factors for T2DM, highlighting the multifactorial nature of this metabolic disorder. We observed that participants who developed T2DM exhibited a cluster of adverse metabolic characteristics at baseline, including higher BMI, larger waist circumference, higher blood pressure, and a less favorable lipid profile. These findings reinforce the understanding that T2DM arises from a complex web of interconnected risk factors, each contributing to the dysregulation of glucose homeostasis. However, the crucial observation is that the association between elevated GIP levels and increased T2DM risk persisted even after rigorously adjusting for these traditional risk factors. This implies that GIP's contribution to T2DM development is independent of, and potentially synergistic with, other known contributors. This finding strengthens the argument for considering GIP as a distinct and significant player in the pathogenesis of T2DM, warranting further investigation and therapeutic consideration. Obesity, particularly central adiposity (excess fat around the abdomen), is a well-established risk factor for T2DM. Adipose tissue, far from being an inert storage depot, is a metabolically active endocrine organ that secretes a variety of hormones and cytokines, many of which can influence insulin sensitivity and glucose homeostasis. In our study, higher BMI and larger waist circumference were significantly associated with an increased risk of T2DM. This aligns with a wealth of evidence demonstrating that obesity increases the risk of insulin resistance, beta-cell dysfunction, and ultimately, T2DM. The interplay between GIP and obesity is particularly intriguing. While obesity can lead to increased GIP secretion, potentially contributing to GIP receptor desensitization and insulin resistance, GIP itself may also contribute to the development and perpetuation of obesity. As discussed earlier, GIP can stimulate LPL activity and lipogenesis, promoting fat storage and contributing to the expansion of adipose tissue. This creates a vicious cycle where obesity leads to increased GIP secretion, which further promotes fat accumulation and exacerbates obesity, increasing the risk of T2DM. Furthermore, obesity is associated with a chronic low-grade inflammatory state, characterized by elevated levels of pro-inflammatory cytokines. These cytokines can interfere with insulin signaling, contributing to insulin resistance. GIP, through its pro-inflammatory effects in adipocytes, may further fuel this inflammatory state, exacerbating insulin resistance and increasing the risk of T2DM. Hypertension, or high blood pressure, is another major risk factor for T2DM. Individuals with hypertension often exhibit insulin resistance and impaired glucose tolerance, increasing their susceptibility to T2DM. In our study, participants who developed T2DM had higher systolic and diastolic blood pressure at baseline. This finding is consistent with previous research demonstrating a strong link between hypertension and T2DM. While the exact mechanisms linking hypertension to T2DM are complex and multifaceted, several factors may contribute to this association. Hypertension can lead to endothelial dysfunction, impairing the delivery of insulin and glucose to peripheral tissues. Additionally, hypertension can activate the renin-angiotensin-aldosterone system (RAAS), which can promote insulin resistance and inflammation. The relationship between GIP and hypertension is less well-defined. Some studies have suggested that GIP may have

vasodilatory effects, potentially counteracting the adverse effects of hypertension. However, more research is needed to fully elucidate the interplay between GIP and hypertension in the context of T2DM development. Dyslipidemia, characterized by abnormal levels of lipids (cholesterol and triglycerides) in the blood, is a common comorbidity of T2DM. Individuals with T2DM often exhibit elevated triglycerides, low HDL cholesterol, and increased small, dense LDL cholesterol particles, all of which contribute to an increased risk of cardiovascular disease. In our study, the T2DM group had a less favorable lipid profile at baseline, with higher total cholesterol, LDL cholesterol, and triglycerides, and lower HDL cholesterol. This finding underscores the strong association between dyslipidemia and T2DM. GIP may play a role in the development of dyslipidemia. As discussed earlier, GIP can stimulate LPL activity and lipogenesis, potentially contributing to elevated triglyceride levels and increased fat storage. Furthermore, GIP may influence cholesterol metabolism, although the exact mechanisms are not fully understood. The interplay between GIP, dyslipidemia, and T2DM is complex and warrants further investigation. Understanding how GIP influences lipid metabolism and contributes to dyslipidemia could provide valuable insights into T2DM prevention and management. A family history of diabetes is a well-known risk factor for T2DM, reflecting the genetic predisposition to this disease. Individuals with a family history of T2DM are more likely to develop the disease themselves, even after accounting for other risk factors. In our study, a family history of diabetes was significantly more common in the T2DM group. This finding highlights the importance of genetic factors in T2DM susceptibility. While the exact genes involved in T2DM predisposition are still being identified, several candidate genes have been implicated, including genes involved in insulin secretion, insulin action, and beta-cell development. The relationship between GIP and genetic predisposition to T2DM is an area ripe for further exploration. Investigating whether genetic variations in GIP or its receptor influence T2DM risk could provide valuable insights into the role of GIP in disease development.[17-20]

4. Conclusion

This longitudinal study provides compelling evidence that elevated GIP levels are an independent predictor of T2DM development in a Spanish cohort, even after accounting for traditional risk factors. Our findings highlight the complex role of GIP in glucose homeostasis and challenge the conventional view of GIP as a solely beneficial incretin hormone. The superior predictive value of GIP over fasting glucose suggests its potential as an early marker for identifying individuals at risk of developing T2DM, allowing for timely intervention. Several mechanisms, including GIP receptor desensitization, promotion of insulin resistance, and contribution to beta-cell dysfunction, may explain the link between elevated GIP and increased T2DM risk. These findings underscore the need for further research to elucidate the precise mechanisms underlying GIP's role in T2DM pathogenesis and to optimize GIP-based therapies for diabetes prevention and treatment. Incorporating GIP measurements into risk assessment strategies and exploring novel therapies targeting GIP signaling hold promise for curbing the global burden of T2DM.

5. References

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