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# Glycemic Index Trends and Clinical Implications: Where Are We Going?

***Índice Glicémico: Tendencias e implicaciones clínicas ¿Hacia dónde vamos?***

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## Abstract

Glycemic index (GI) is currently considered as an alternative system that classifies food according to the carbohydrate quality (CHO), measuring its absorption speed; meanwhile, glycemic load GL is a more recent term that relates the quality and quantity of the CHO per gram of the usual consumption portion. Glycemic index and glycemic load reduce the post-prandial glycemic impact without the total restriction of CHO in the diet. Initially, GI was used only in patients with diabetes, currently it is also considered as a risk indicator in other pathologies. However, there is great controversy due to an inaccurate interpretation of the knowledge about the methodology used for its determination. The aim of this review is to elucidate this current debate and to expand the relationship between the GI and the risk of diabetes and other chronic diseases; thus, highlighting new prospects for its applicability in the dietary intervention for diabetic athletes and in the production of functional food designed for patients with diabetes. There is strong evidence that this indicator has become an innovative system for various multidisciplinary health programs.

**Key words:** glycemic index, diabetes, chronic diseases, functional food.

## Resumen

Actualmente el índice glicémico (IG) se considera como un sistema alternativo que clasifica los alimentos según la calidad de los carbohidratos (CHO), midiendo su velocidad de absorción; por otra parte, la carga glicémica (CG) es un término más reciente que relaciona la calidad y la cantidad de CHO por gramo de la porción de consumo habitual. El índice glcémico y la carga glucémica reducen el impacto glicémico posprandial sin la restricción total de CHO en la dieta. Inicialmente, el IG era utilizado solo en pacientes diabéticos, actualmente también se considera un indicador de riesgo en otras patologías. Sin embargo, existe una gran controversia debido a una interpretación incorrecta del conocimiento sobre la metodología utilizada para su determinación. El objetivo de esta revisión es dilucidar este debate actual y ampliar la relación entre el IG y el riesgo de diabetes y otras enfermedades crónicas; así, se destacan nuevas perspectivas de su aplicabilidad en la intervención dietética para deportistas diabéticos y en la producción de alimentos funcionales diseñados para pacientes con diabetes. Existen fuertes evidencias de que este indicador se ha convertido en un sistema innovador para varios programas de salud multidisciplinarios.

**Palabras claves:** Índice glicémico, diabetes, enfermedad crónica, alimentos funcionale

## Introduction



The glycemic index (GI) is an alternative system that allows the numerical expression of available carbohydrates effect of a food on glucose concentrations[1], representing a measure of the average glycemic value following the ingestion of a food, usually 50 g of carbohydrates available for a given period of time of 2 or 3 hours[2,3] expressed as a percentage in relation to a standard food (glucose or white bread). Glucose is considered a reference product with an attributed GI of 100[4,5]. By replacing a high GI food with a lower GI food a decrease in glycemia is generated, providing a way to express the potential glycemic effect of a meal or snack. Foods with carbohydrates capable of being digested, absorbed and metabolized rapidly are considered of high GI ≥70 on the glucose scale. Those between 55-70 are considered of intermediate GI, while those with low GI correspond to a value ≤55. The glycemic load (GL) is the result of the GI and the total amount of carbohydrate available according to a specific portion of food[1,6]. In this sense, the GI classifies the foods according to the quality of carbohydrates (CHO), measuring their speed of absorption; In terms of GL is a more recent term that relates quality and quantity of CHO per grams of usual consumption portion.

Both indicators allow reducing the postprandial glycemic impact without the total restriction of CHO in the diet. The GI tables for food were developed in 1995 and later updated in 2002 and 2008[1,7]. There is a great controversy due to an inaccurate interpretation of the tests to determine the GI, being the objective of this review to elucidate the reasons that explain this current debate, to extend the relation between the GI and the risk of new chronic diseases and to highlight the novel perspectives of its applicability in physical exercise and in the food industry.

## Methodology

A bibliographic search was performed to retrieve relevant articles published from 5 February to May 2018 from scientific searchers (PUBMED, EBSCO, Scielo and Scopus) to analyze articles that included keywords (glycemic index / glycemic load / risk / diabetes / obesity / cancer / renal / epilepsy / physical activity / functional products). Four researchers in English and Spanish performed manual review of the articles. Randomized studies, control cases, and intervention studies were included in the search for articles that make up this review. Evidence indicates that the usefulness of GI values for managing chronic disease risk remains controversial. Wolever TM, one of the creators of this system, claims to be as reliable as the value of macronutrients in food labels[8]. Despite its controversial use, this indicator has been included in the guidelines of dietary recommendations for the population in Nordic countries[9] and Italy[10]. Even though most of the world's dietary associations have not considered this tool among their nutritional guidelines, the European Association for the Study of Diabetes, the American Diabetes Association, the Canadian Diabetes Association and the Diabetes Nutrition Subcommittee of the UK have rated CHO quality management as a priority within their recommendations[11,12,13,14]. Specifically, the International Diabetes Federation recognized the relevance of post-prandial glucose regulation for achieving glycosylated hemoglobin (HbA1c) targets through the development of specific guidelines, the management of which is linked to the concept of GI[15].

**Controversy on the methodology**

Most current criticisms point to high glycemic variability in healthy adults. In this regard, a study with 63 healthy subjects examined intra and interindividual variability (CV) in the glycemic response, as well as methodological and biological factors that potentially mediate this response. CV was 20% and 25%, respectively.

Among the biological factors evaluated, the insulin index and the HbA1c values explained 15% and 16% of the variability in the mean value of GI for white bread, concluding that there is a high variability in the individual response to the determination of the value of GI. This group of authors classifies GI as an inappropriate approach to guide food selection[16]. Recent reviews have been based on concerns about the validity of this indicator, in the hypothesis that it cannot predict the glycemic response, or about the alleged imprecision of the methodology[2,17], in addition to that it is not possible to estimate the value of the GI in mixed meals[18,19], and that many factors influence the results. In response to these premises, the last consensus of experts in GI[1], concluded that most of the current criticisms are not valid, reflecting a failure in the translation of knowledge[6,20]. Some premises, for example the GI of the subjects change daily, are based on the misuse of the term "GI" as if it were synonymous with "glycemic response" (GR). "GI" is not "GR" and therefore care must be taken to use the terms correctly.

The initial central methodology used to measure GI has not changed, therefore to improve accuracy, a series of procedures were modified[3]. If the GI is methodologically correctly used, it is sufficiently accurate to distinguish between high GI (HGI 70) and low GI (LGI 55) foods on the glucose scale with 95% certainty[6]. Alternative terms include "GR" or "Relative GR". It is not necessarily expected that the calculated GI of mixed foods will predict their glycemic response, since the glycemic impact of these foods depends not only on their GI, but also on the amounts and types of lipids, proteins and CHO contained in the diet. On the other hand, the GI is a property of foods rich in CHO, so it is not appropriate to measure this indicator in this type of food. In these cases, this value must be determined from the GI of the carbohydrates, foods or ingredients in the food and calculated in the same way as the GI average of a diet is quantified[6]. A number of critics have raised the objection that many factors, such as variety, processing and cooking, influence the GI of a food. In fact, these factors affect it but this is not an argument against the use of this indicator; rather it is a cause that is useful as another tool to quantify the impact, as postprandial glycemia serves as an indicator of risks in various pathologies[1].

**Glycemic index as a risk marker of diseases**

There is strong evidence of the relevance of GI in some diseases such as diabetes[21] cardiovascular diseases[22], cancer and even for body weight control[1].

These trends were confirmed recently in men and women, with greater risk reduction in the latter[23]. Reduced risk of coronary heart disease, as well as the risk of certain types of cancer, mainly breast and colorectal, have been demonstrated with low GL and GI diets in women, although not all studies have shown these benefits[26,27,28]. There are investigations that relate the modification of risk factors for these diseases together with the GI of the diet[1]. Studies from a large meta-analysis have shown that low-GI diets significantly improved glycemic control[23] and LDL-cholesterol[29], even though there are not many studies with proven changes in HbA1c, some clinical trials have shown significant decrease in C- reactive protein[30,31,32]. Another review identified a total of 37 prospective cohort studies of GI, GL and risk of chronic disease. Low GI and / or low GL diets are independently associated with a reduced risk of certain chronic diseases. In diabetes and cardiovascular disease, protection is comparable to that observed for fiber intake.

The findings support the hypothesis that increased postprandial glycaemia is a universal mechanism for the progression of the disease[33].

**Type I and Type 2 Diabetes**

Despite the difference in glycemic curve stability in subjects with diabetes type 2 (DM2) compared to healthy subjects, several studies have indicated the association between nutritional status and glycemic variability in individuals with this pathology[34,35,36]. However, few well-controlled investigations have exhaustively examined the effects of very low carbohydrate diets on this condition.

In a meta-analysis, 10 randomized trials were considered in 1376 participants comparing diets containing low to moderate amounts of CHO (<45% energy) v/s diets containing high amounts of this nutrient in subjects with DM2. The greater the restriction of carbohydrates, greater the effect of the decrease in glucose (R=-0.85, p<0.01). However, HbA1c was similar in the second group of dietary intervention post-1-year, concluding that low to moderate carbohydrate diets have a greater effect on glycemic control. In addition to this decrease HbA1c in short-term, there is no superiority of carbohydrate-restricted diets in terms of glycemic, weight or LDL cholesterol control[37]. In another report of multivariable regression analysis in a cohort of 3918 Chinese adults, was correlated the GI, GL and glycemic homeostasis and evaluated the hypothesis that these associations may be modified by their genetic predisposition or if there are any combined effects with the intake of dietary fiber present in cereals. This relationship was more pronounced among people with a high genetic risk of DM2 or with a low intake of cereal fiber, evidencing that these indicators exert relevance in the glycemic homeostasis of this population, particularly among the individuals genetically predisposed to DM2[38]. In a cross-sectional study of 640 patients with DM2, associations of GI, GL, intake of CHO and fiber with hyperglycemia were investigated. The elevated GL of the diet was associated with an increased risk of this complication in these subjects. GI was not significantly associated with elevated fasting plasmatic glycaemia (FPG) or HbA1c. The higher intake of dietary fiber was associated with a lower risk of increased FPG but not with a lower risk of HbA1c increased. GL and CHO intake were positively associated with the risk of hyperglycemia in type 2 diabetic patients. A meta-analysis of prospective cohorts finding consistent with the protective effects of GI and dietary GL, quantifying the range of ingestion associated with a minor risk[39].



**Gestational Diabetes Mellitus**

A study of 9 randomized controlled trials evaluated the effects on pregnancy of 11 types of dietary counseling for women with gestational diabetes mellitus (GDM); 429 mothers and 436 infants, including high, low and moderate GI foods, high amounts of monounsaturated fats and fiber, were included compared to the standard recommended diet of ADA. No significant differences were observed in macrosomia for gestational age[40]. Another meta-analysis of 11 trials involving 1985 women and 11 newborns examined the maternal and neonatal effects of low GI diets comparing healthy pregnancies and those diagnosed with GDM. In 8 trials, gestational weight gain, fasting blood glucose, birth weight, weight index, macrosomic ratio and gestational age were investigated (Big for gestational age, BGA). Low GI diets significantly reduced fasting and post-prandial glucose and BGA ratio[41], concluding that low GI diets may have beneficial effects on maternal outcomes for those at risk of developing high glucose levels without causing adverse effects on newborn outcomes. Another study reported the comparison of the effects of a general dietary intervention and another with low GL on glycemic and lipid control in pregnant women with GDM. The intensive intervention of low GL in two groups of mothers with 2 and 26 weeks of gestational age respectively.

Significantly decreased energy intake, lipid and carbohydrate consumption, without affecting body weight gain, birth weight or other maternal-fetal outcomes. Low GI dietary intervention outperformed the other intervention in glycemic control and improved lipid levels in women with GDM[42].

### Dyslipidemias and heart diseases



In a random effects meta-analysis, twenty-eight trials comparing low and high GI diets for 4 weeks in 1272 participants, concluded that this type of diet reduces total and LDL cholesterol without affecting HDL cholesterol or triglycerides[29]. In a systematic review and meta-analysis of 14 randomized controlled trials, associations of GI and GL were determined with systolic blood pressure and diastolic blood pressure in 1097 healthy subjects for 6 weeks, concluding that a lower GL diet can lead to significant reductions in blood pressure. In another study of 44099 participants, the GI and GL variables of the diet were correlated with the risk of stroke in the large EPIC-Italy (EPICOR) cohort; associating significantly diets of high GI and high GL with the increased risk of stroke, both hemorrhagic and ischemic. Concluding that in this Italian cohort, the consumption of foods with high GI and GL increased the overall risk of stroke[43].

### GI and obesity

In a low-GI dietary intervention in 20 obese individuals, there was an increase in fat use during exercise, regardless of changes in energy expenditure, which highlights the therapeutic potential of low GI foods to reverse metabolic effects in obesity[44].

Another controlled study with 19 subjects indicated that a low GI diet along with 12-week exercise would increase the expression of fat transporters and oxidation in skeletal muscle resistant to insulin, evidencing a weight loss of 8% to 10%, improvement in insulin sensitivity and molecular mechanisms of skeletal muscle.

These effects were independent of the GI of the diets[45]. In another study with 30 healthy controls, it was found that high GL food significantly increased blood glucose levels, especially in overweight individuals[46]. In a review discussion, several epidemiological and intervention studies show an evident relationship between GL and the development of DM2, as well as GI on body weight, triacylglycerides, HDL-cholesterol, C-reactive protein (CRP) and protein glycation.

On the other hand, the beneficial effects of long-term interventions through the administration of low-GI / low-GL diets relative to basal insulin and CRP may be useful in the primary prevention of other obesity-associated diseases[48,49].

### GI in menopause and depression

Low circulating levels of sex hormone binding globulin (SHBG) have been shown to be a direct and strong risk factor for DM2, heart disease and hormone-dependent neoplasms. In a study of 11,159 menopausal women in whom GL, GI, fiber, and high specific food intake were evaluated, low GL / GI diets with low sugar content and high fiber content were found to be associated with higher serum concentrations of SHBG levels among postmenopausal women[50]. In another prospective 3-year study of 69,954 postmenopausal women, depression, GI, GL and specific carbohydrate intake (added sugars, total sugars, glucose, sucrose, lactose, fructose and starch) were correlated, concluding that high GI diets could be a risk factor for depression in this population subgroup, suggesting randomized trials to determine whether low-GI diets could serve as preventive treatments for depression in these women[51].

### Dietary glycemic index, glycemic load and cancer

A review demonstrated the association between GI and GL, with the risk of suffering from several types of neoplasia[27], strongly evidencing the high GI of the diet with the risk of colorectal cancer, and high GL with breast and endometrial cancer[27]. Specifically, a relative risk of cancer was found with the following number of studies per organ with a 95% confidence interval: (19 breast, 68 colorectal, 10 endometrium, 10 esophagus, 4 hepatic, 4 ovary, 5 pancreas, 10 prostata, 6 stomach[27]).

It is believed that the main mechanism of these associations is chronic hyperinsulinemia[52, 53,54]. Insulin behaves like a mitogen and could also increase the bioactivity of insulin-like growth factors that can promote cancer by inhibiting apoptosis and stimulating cell proliferation. In a meta-analysis, six cohort studies and two case-control studies, with a total of 5,569 cases including 1,290 women with endometrial cancer and 1,436 controls, a moderate positive association was observed between GI and risk of this type of cancer, but was not associated with elevated GL in the diet. The pooled results of the observational studies, including the control cases, provide evidence of a modest positive association between high GL but not GI and the risk of this pathology[55]. In another meta-analysis of 10 prospective studies of 15,839 cases and 577,538 participants, the GI and GL were associated with the risk of breast cancer finding a relative risk with 95% confidence intervals. These associations were modified by geographic region, follow-up period, number of cases or initial menopausal status, suggesting that high GI in the diet and not so the GL of the diet is associated with a significantly higher risk of breast cancer[56].

### Glycemic Index as Epilepsy Treatment

In a study of 36 patients with epilepsy who received low-GI dietary treatment for one year, the frequency of seizures was effectively reduced, although the freedom of episodes was only reduced by 2%, considering it as a therapeutic option for drug-resistant epileptic patients[57]. Epilepsy is known to be a common feature of Angelman syndrome and seizures are often refractory to multiple medications.

Through a retrospective review of the medical record of 23 subjects who used this type of treatment at the Center for Dietetic Therapy of Epilepsy in Massachusetts and in another small trial published by Thibert, concluded that high seizure control and low-profile of secondary effects make the low GI diet an excellent alternative to antiepileptic drug therapy in patients with this syndrome[58]. Another study with 42 children diagnosed with refractory epilepsy, they were given a diet consisting of 65% fat, 25% protein and 10% carbohydrate (40-60 g) with a GI <50. A seizure reduction of more than 50% was observed in 71.4% patients after 15 days, in 73.8% and 77.8% at the end of the first and second month respectively, without significant complications, therefore it is suggested as a safe adjuvant antiepileptic therapy as an alternative to the ketogenic diet in conditions in which it cannot be used, particularly in those who find this treatment effective but with a high degree of intolerance[59].

**Glycemic indicator and glycemic load of functional products for diabetics**

Currently the food industry has created a large quantity of products with different bio-active components such as soluble fiber with a determined GI and GL. These products specialized in preventing or treating various diseases, and have been classified as “Functional”. A growing number of these products can be used in diabetics, especially in DM2, to regulate glycemic control[60,61]. Liquid or solid products for mass consumption[7], and even novel sweeteners have been studied recently[62]. One of them is the natural isomaltulose disaccharide which can be produced commercially from sucrose (beet sugar) on an industrial scale, used in various food and beverage, as well as in special nutritional foods and enteral formulas as a food ingredient and alternative sugar[60,61,63]. The applicability of the GI in the nutritional label of foodstuffs is currently a controversial premise, groups of authors debate whether it is really favorable[8] or not to include this indicator in the food labeling. In this regard, an article commented that the contrary position of Health Canada (HC), is scientifically invalid. HC concluded that the GI has poor accuracy for labeling based on incorrect application of the standard deviation.

However, the GI methodology is sufficiently accurate to distinguish, with high probability, low GI (≤55) or high GI (≥70) foods and to approve the procedure required by the Canadian Agency’s Nutrition Compliance Test Inspection of Food[2].

Until 2013, Canadian consumers could only access to unregulated and misleading GI information. Well-designed guidelines for the labeling of this indicator would provide consumers with accurate information and help them choose healthier foods[2]. If this information were to be extended in most food-producing countries, a great alternative could be generated in food education at large scale.

**New perspectives of ig and physical activity**

Several studies have evaluated the usefulness of GI in exercise on different metabolic markers[64,65]. GI management has been reviewed to improve the first and second phases of glycogen recovery, glycogen loading and metabolism during exercise, including the control of rebound hypoglycemia as well as the stimulation of lipid oxidation[44], confirming that it may influence adipocyte lipolysis, plasma free fatty acid levels and CHO oxidation rates. However, at functional level, the results have been inconsistent, with evidence of better exercise performance in some studies, but not in others[66]. A meta-analysis of 15 cross-over and randomized trials compared the effect of carbohydrate pre-exercise meals of low glycemic (LGI) and high glycemic index (HGI) on subsequent exercise performance in healthy subjects; basing the theory that resistance during exercise post LGI meal is superior[67]. There is currently no consensus as to whether CHO consumption of different GI improves performance[68]. There is evidence that increased muscle glycogen resynthesis demands food with CHO of HGI. However, recent investigations indicate the interaction between CHO, LGI and fat oxidation[68]. In another study with 32 men, who followed 1 week of controlled overeating, 3 weeks of calorie restriction, and 2 weeks of hypercaloric feedback from low v/s high GI; the adaptation of fasting macronutrient oxidation and the ability to suppress fat oxidation during an oral glucose tolerance test were measured, concluding that both the high GI as well as the high CHO content affect the oxidation of the substrate and, therefore, allow the recovery of body weight in healthy men; Arguing in favor of a lower GL diet for maintenance of post-weight loss[69]. Actually, this indicator has been useful in evaluating different commercial products, such as sports drinks on the use of metabolic substrates in the postprandial state and their relationship with performance and resistance during exercise[70]. In addition, few studies were made on athletes with diagnosis of DM1 and DM2 in relation to the GI. For DM1, exercise can cause hypoglycaemia. To avoid it, a carbohydrate-rich meal should be eaten 1 to 3 hours before exercise with a reduced insulin dose.

During the activity, at least 40 g of glucose per hour should be ingested and should be increased if the insulin dose is not reduced. After exercise, it is important to rebuild glycogen stores to reduce the risk of hypoglycemia. Despite these difficulties, exercise is recommended in DM1 and high competition exercise is, also, possible. Improved insulin sensitivity, reduced body weight and cardiorespiratory effects are evident in DM2[71]. Carbohydrates should only be given to prevent hypoglycaemia[71].

**Utility of the glycemic index in health programs**

There are several studies in the management of weight and glycemic profile [72] through specific interventions towards the quality of CHO in the diet. Start Start is a randomized controlled trial that assigns overweight and DM2 patients into two groups: 1) medication management and self-care counseling; 2) low CHO loading with pharmacotherapy. It is hypothesized that the last one will improve the glycemic profile, reduce hypoglycemia, diabetes medications use and weight in relation to medication and self-care counseling, regarding the standard management[73]. In another randomized controlled trial of 162 diabetics, was determined the long-term effects of a program with changes in the quantity or source of CHO on life quality, symptoms and dietary satisfaction in patients with DM2; assigned to diets differently distributed, high content of carbohydrate/high-glycemic-index (HGI) diets, high-carbohydrate/low-glycemic-index diets, or lower-carbohydrate/high-monounsaturated-fat for 1 year. HbA1c levels had less increment in those patients who gained less weight, had less increased appetite and were more satisfied from eating. Although overall dietary satisfaction was higher on 40% of carbohydrate diets than on the 50% of carbohydrate diets, LGI diet was no less satisfying than HGI diet[74] The DEDICA clinical trial in Italy will evaluate the combined effect of a low GI diet, moderate physical activity and vitamin D supplementation on breast cancer recurrence in a mediterranean lifestyle in 506 women for 1 year followed by 33 months[75], according to their authors, this novel intervention program promises to reduce the rate of recurrence of this type of pathologies. It is important to consider the effect of physical activity on health, as it is one of the protective factors against the development of obesity, thus justifying the generation of intervention programs that allow compliance of physical activity recommendations according to the target population, which ideally should begin in childhood in order to avoid the development of pathologies associated with overweight in adult life[76]. Likewise, in specific pathologies such as gestational diabetes, moderate physical activity was also directly correlated with the decrease in the risk of suffering it, as was demonstrated in a cross-sectional study in 579 pregnant women in Colombia[77]. Finally, Studies of multidisciplinary programs, such as Star Star[73] and DEDICA[75] allows to clarify the current relevance used for this indicator in the multidisciplinary health programs, specifically focused on bio-medical and nutritional care directed to different study groups.



## Conclusions

Given the controversy that GI produces, especially on methodological aspects, the last consensus of experts on this topic, concluded that most of the current criticisms are not valid, but reflect a failure of the knowledge expansion. Certain global associations have included this indicator in their guidelines, endorsing it as an important dietary tool. There is strong evidence suggesting the potential relevance of GI as a new risk marker for various pathologies; not only in the different types of diabetes, but also in certain heart diseases, 9 types of neoplasias and in weight control; recently associating it with other diseases such as epilepsy, menopause and depression. Some of the new perspectives on the applicability of this indicator focus on the dietary intervention in athletes to improve resistance in training. Future research might relate it to diabetic athletes to avoid rebound hypoglycemia during high-competitive sports. Another approach considers it a panacea for the food industry, especially for functional foods and a novel system for various multidisciplinary health programs.

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