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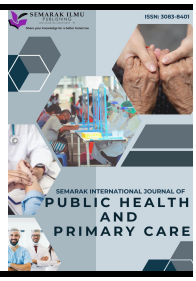

Insulin Index – A "Decretin" Approach in the Era of "Incretin"

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ABSTRACT

Obesity and diabetes have become prevalent health issues globally, with significant impacts on the Asian population, including Southeast Asia. This paper explores the concept of "decretin," which focuses on minimising insulin secretion through dietary strategies. This concept is in contrast to the incretin-based approaches that enhance insulin release. The Insulin Index (II), which measures the insulin response to various foods in comparison to a reference food, is proposed as a tool that may be manipulated for the preferred decretin action. Decretin involves dietary strategies to reduce insulin excursion, potentially offering therapeutic benefits for insulin resistance and diabetes. This paper emphasises the discussion of foods with low II values, insulin responses, and the strategies for insulin resistance and hyperinsulinemia. This may open further research pathways on the decretin action to develop tailored dietary guidelines for diabetes management in the Southeast Asian region.

1. Introduction

In today's world, obesity and diabetes have both become common household names. The Asian population is no stranger to these medical conditions. In fact, China, India, and Pakistan held the top three spots with the largest number of diabetics worldwide as of 2021 [1]. In Southeast Asia (SEA), Brunei and Malaysia had the highest prevalence of obesity of more than 50% [2,3]. Malaysia in particular saw a rise in 2019 compared to previous national surveys conducted in 2011 and 2015, respectively [3].

The concept of "incretin" has gained significant attention in recent times in the context of obesity, weight loss and diabetes management [4-6]. Presently, obesity management is centered around bariatric surgery, GLP-1 receptor agonists, sympathomimetic agents, opioid antagonist with dopamine and noradrenaline reuptake inhibitor, lipase inhibitors, physical activity, and the combination of pharmacotherapy with other treatment modalities [7]. Nevertheless, GLP-1 receptor agonists such as semaglutide which is essentially an incretin, have appealed to many obese patients and owes its growing popularity to celebrity endorsements and its effectiveness in causing weight loss [8].

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The concept of "decretin", on the other hand, offers an intriguing alternative approach. There is an apparent research gap where the focus has been on increasing insulin secretion to enable better blood glucose control, when excess insulin is in fact detrimental in various ways. This can be explained by hyperinsulinaemic states which carry the burden of multiple disease states including but not limited to insulin resistance, cardiovascular diseases, cerebrovascular events, and obesity [9,10]. Hence this research has a significant role of realigning the focus towards tackling insulin resistance through a decretin concept of taming insulin spikes. This short communication paper aims to explore the concept of the Insulin Index (II) and its potential as a tool for managing diabetes, particularly in SEA.

2. Throwing Light on Decretin

Decretin, an emerging concept, refers to minimising insulin secretion, which includes dietary strategies to downscale insulin response to food intake, in contrast to the incretin-based approaches that enhance insulin release. The term decretin was used back in 1997 by Ensinck *et al.,* [14] and was later discussed separately by previous researchers [11-13]. To our best knowledge all these scientific discussions were from animal models and the concept in human endocrinology is yet to be established. However, the concept of decretin is gaining traction as a potential therapeutic approach to manage insulin resistance and diabetes [15-17].

Current focus on decretin only involves limostatin and neuromedin U (NMU) that suppress insulin secretion [12,18]. Its multiple roles revolve around food intake suppression, energy expenditure and locomotor activity stimulation, improvement in glucose metabolism, increase in BAT thermogenesis, and decrease in both adiposity and body weight [18]. We believe that the unique physiologic, endocrine and neurological properties of the decretin action would result in an alternative means to the desired endogenous insulin suppression.

3. Hyperinsulinaemia – The Ticking Timebomb

Hyperinsulinaemia, which was discussed extensively by Kraft *et al.,* [21] and Croft *et al.,* [20] is a known early biomarker for metabolic dysfunction and metabolic disease. It is state of chronically elevated blood insulin owing to insulin secretion dysregulation with or without poor clearance, and in the absence of hypoglycaemia [22]. A substantial body of evidence has suggested that hyperinsulinaemia is well-linked to a myriad of medical conditions such as Type 2 diabetes, obesity, cardiovascular disease, cerebrovascular events, premature deaths, and even malignancies [9,10].

4. Insulin Index and Decretin: Mechanism of Action

The Insulin Index (II) is a measure that quantifies the insulin excursion elicited by various foods in comparison to a reference food such as bread or glucose [23]. While the Glycaemic Index (GI), which measures blood glucose levels, the II provides insight into how different foods impact insulin secretion [23–28]. For perspective, the differences seen between the post-prandial blood insulin and glucose excursion curves of watermelon are showcased in Figure 1. The post-prandial glucose's incremental area under the curve (iAUC) of the test food, watermelon in this case, appears to be well below that of the reference food which is glucose. This results in a low to moderate GI value of watermelon. On the contrary, the post-prandial insulin's iAUC of watermelon appears to be almost that of the reference food. This indicates that the II of watermelon is close to 100. Figure 2 shows the hypothesised decretin action of the food with low II on both the glucose and insulin excursions after

consumption. The decretin food chosen for the illustration has both low insulin and glucose excursion. This was compared with a standard reference food in clinical nutrition and the incretin response as well. The orange and light blue arrows show the incretin effect and decretin action, respectively. A previous compilation of II and GI values showed that less than 1% of food with II lower than 50 were in the high GI group [26]. In addition, there were no representation in the medium and high GI group when food had II lower than 20 [26]. Taking account, the compilation was limited to 121 foods, we hypothesise that decretin action would lower both the insulin and glucose.

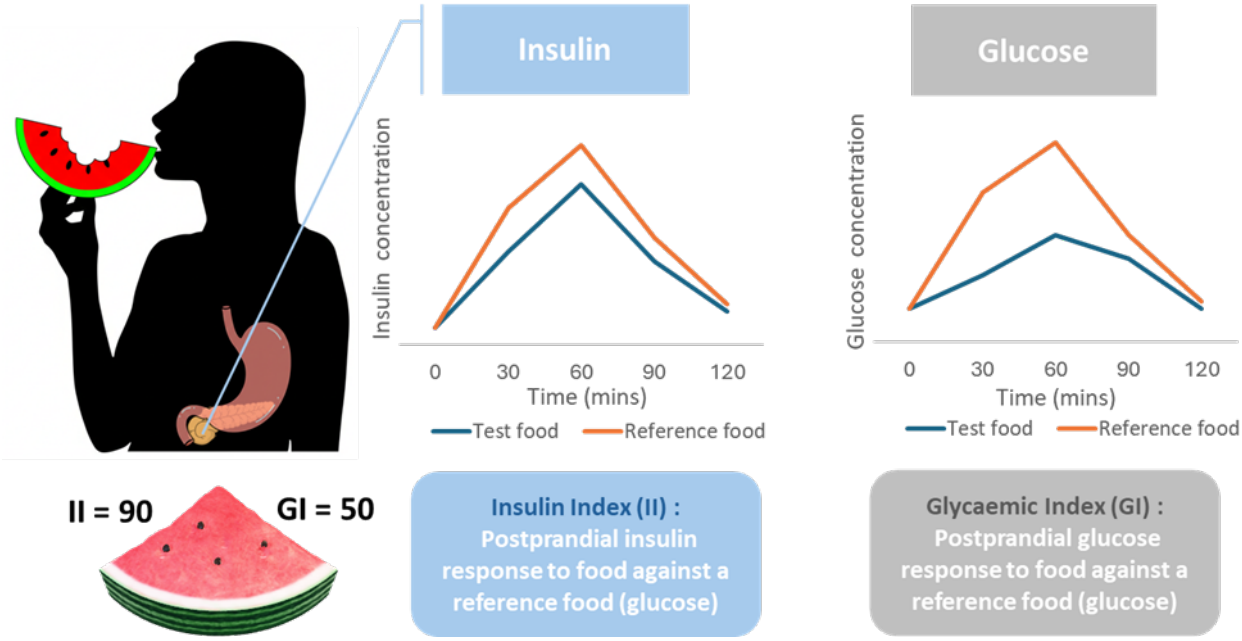

Fig. 1. The difference in post-prandial excursion curves between blood insulin and glucose for watermelon, and its respective II and GI values (data adapted from Ryu et al., 2012) [29]

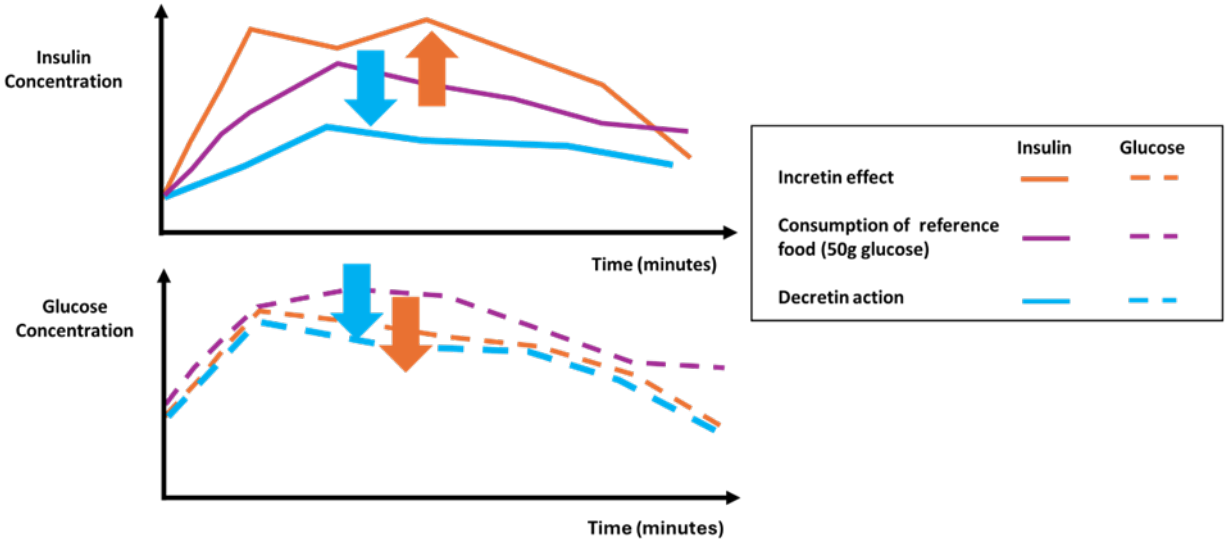

Fig. 2. The incretin effect and decretin action on both insulin and glucose excursions

While there are neither clinical cut-off points nor ranges for low II, foods with low II values cause smaller insulin excursions. The mechanism involves lowering of overall insulin excursion, inflammation and reduced deposits of ectopic fats and reduce occurrence of non-alcoholic fatty liver

disease (NAFLD) and atherosclerosis [15,29,30]. The recent II compilation from Hendricks et al., shows that the insulin excursions vary significantly between foods, suggesting that selecting foods with low II may play a role in managing insulin spikes effectively. To date, two trials have examined the effects of a low II diet on health outcomes [31,32]. These studies suggest promising results as they have explored the lowering of insulin excursion and reducing the risk of being overweight [31,32].

5. The Decretin Effect of Low II Foods

Creating a comprehensive low II food list requires identifying foods that elicit minimal insulin excursions. These foods typically include nuts, seeds, fats, and certain protein sources. Figure 3 is a simplified diagram of some foods within specific II cutoff points based on a recent II compilation [15].

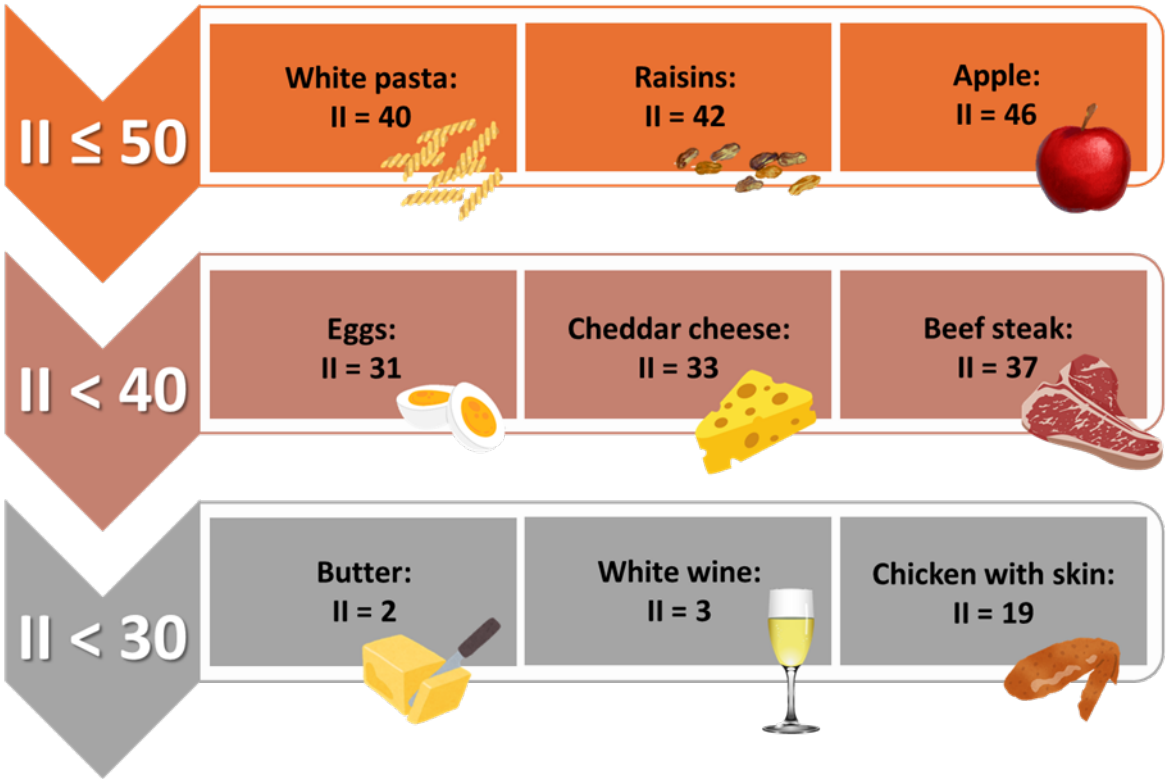

Fig. 3. Some foods that are below the II of 50. Illustration modified from Hendricks *et al.,* [15]

Interestingly, we found that most Mediterranean foods, characterised by high consumption of fish, nuts, and healthy fats, are likely to have a low II. We hypothesise that, decretin action may have contributed to the health benefits associated with the Mediterranean diet which has yet to be probed in the field of clinical nutrition [33]. From our food II compilation, salient Mediterranean foods such as durum wheat-based pasta, tomato pasta sauce, wine, cheese and olive oil had lower II than other foods [15].

On the other hand, certain foods have a high capacity to spike insulin levels, such as sugary snacks, refined carbohydrates, vegetables, fruits, and dairy products. Identifying and minimising these foods is crucial for managing the insulin spikes post-meal [15,23].

6. The Southeast Asian Diabetic Clusters' Dilemma

In recent years, clustering diabetes has been revolutionary in providing more insightful, precise and personalised management [34,35]. In SEA, the dilemma of managing diabetes is compounded by a lack of region-specific II data and the prevalence of incretin-based medications. The minimally populated II lists pose a challenge for developing dietary guidelines tailored to local populations. In SEA, diabetes clusters, predominantly related to obesity and insulin resistance (IR) [36,37].

We speculate that there is a role of decretin to "tame" the hypersinsulinaemic responses. Although there are no clinical cut-off points for low-, medium-, and high-II, foods that exert low insulin response may potentiate the decretin action. To back our hypothesis, we have discussed in this manuscript's earlier subtopic about the II-GI relationship from Bao *et al.,* [26]. Future studies should be carried out to test this hypothesis thus strengthening or nullifying the decretin hypothesis.

7. When Decretin Interacts

The impact of the insulin on other hormones, such as glucagon and may provide deeper insights into the holistic management of diabetes [6,38]. It is now understood that one of the many strategies for regenerating the pancreatic beta-cell, reducing adipogenesis and inflammation of both the pancreas and liver is to re-establish the loss oscillatory properties of insulin and glucagon [39-45]. From an anorexic perspective, the decretin mimics the incretin effect [46-51] . This was also seen in NMU as discussed elsewhere [18]. Foods with low II also affect ghrelin, cholecystokinin (CCK), leptin, and satiety owing further to the anorexic effect [48,52-54]. It is crucial to understand the entero-insular effect of these hormones [45].

8. Conclusion

The concept of the II and the decretin approach seems appealing and entrenched from our discussion. Both offer promising avenues for managing diabetes, especially in SEA region where there are high prevalence of obesity and insulin resistance. It is of paramount importance for future research to expand on the decretin action of food II for as an adjuvant dietary guideline for diabetes management.

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