



Diabetes, Immunity and Defense System: A Paradox in Treatment

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Abstract

Hyperglycemia has been the primary metabolic condition for the origin of diabetic complications. The glucose in the cell is underutilized due to diminished entry of glucose into the cell and down-regulation of the Pentose Phosphate Pathway. The PPP is the potential pathway in maintaining the defense of the cell through GPx, GR, GSH, and GSSG. Particularly, GPx and GSH levels diminish in diabetes. Constipation in diabetes also plays an important role in decreasing the immune system as the excess glucose in the gut lining enhances the number of gut bacteria and fungi. Antioxidants have not been proved to enhance the immune and defense of cells in diabetes but the exhibitory roles of herbal medicines have been potential in exaggerating the immune and defense system by their unknown modulators and enhancers molecules. Turmeric and black pepper have been proven to enhance the immune and defense of the body in diabetics.

Keywords

Pentose Phosphate Pathway (PPP), Glutathione Peroxidase (GPx), Glutathione Reductase (GR), Oxidised Glutathione (GSSG), Reduced Glutathione (GSH)

Introduction

Hyperglycaemia, the excess glucose levels, is the main upheaval for altering the metabolic functionaries inside the cell. The body resists the excess fats and proteins but cannot resist the excess glucose prolonging to make the blood viscous, a restriction in the blood flow, which results in stress for the heart to pump out the blood for circulation [1-3].

The glucose toxicity in diabetes is well documented and explained [4], with the generation of free radicals and their products [5], generation of Amadori products during the process of glycation [6], a decrease in defense and immune system [7], are such primary determinants responsible for causing diabetic

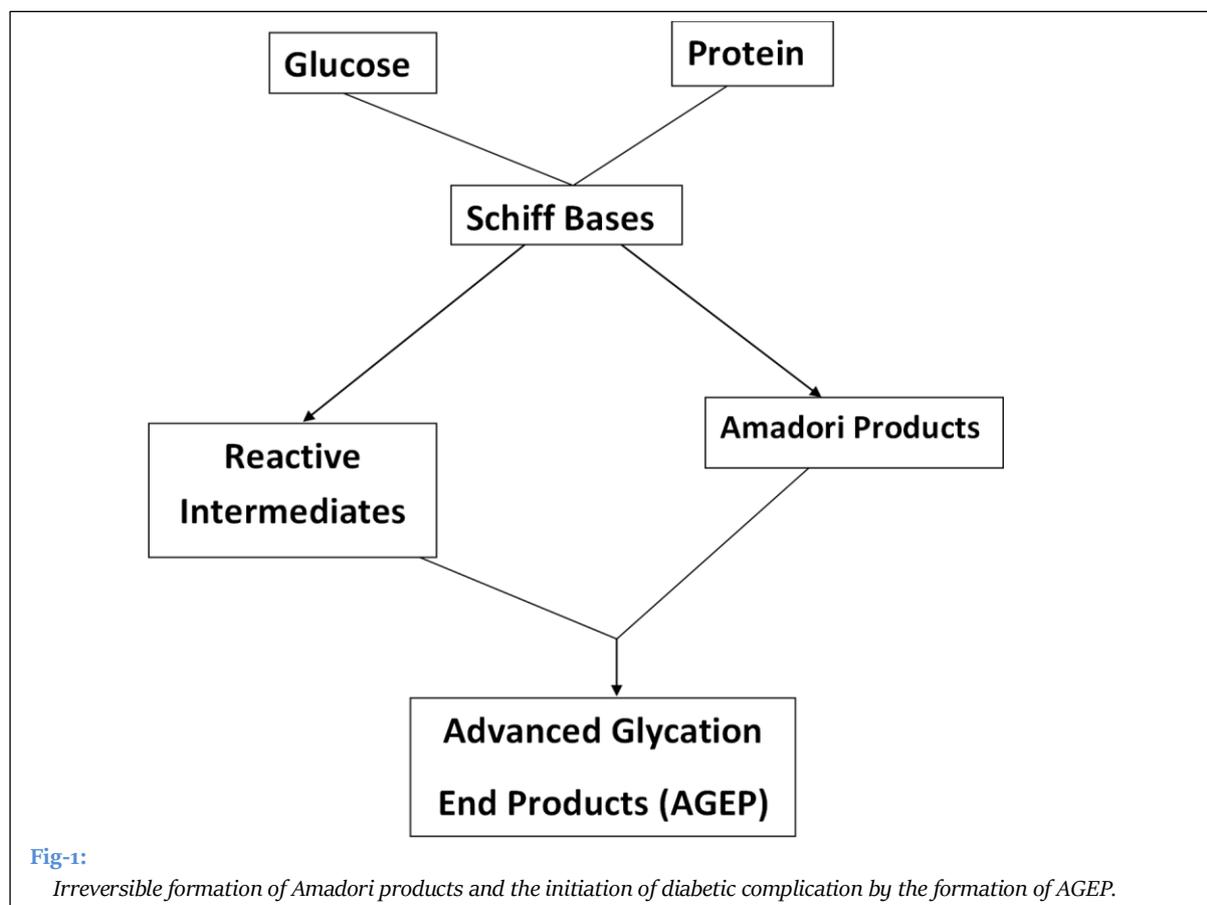
complications otherwise diabetics cannot die before scheduled age [8]. These processes of generation make each and every tissue becoming fragile especially the red blood cells and neural networks [3,9]. The red blood cells in diabetes are greatly damaged due to lipid peroxidation and glycation of hemoglobin [10]. The oxygen carrying capacity of red blood cells is decreased [11]. The glycated hemoglobin becomes an indicator of glucose control over the period of time during diabetes [12]. The sitting of glucose on proteins, lipids, and even carbohydrates irreversibly in the cells and tissues, and the formation of Amadori products become the hallmark in the origin of diabetic complications (**Fig-1**) [13]. As the glucose is being utilized by each and every cell passing through the glycolytic pathway wherein

enzymes are glycated, the pathway gets down-regulated resulting in underutilization of glucose [14].

Pentose Phosphate Pathway and the Defense System

It has been observed that the Pentose Phosphate Pathway in which 10% of the body glucose is being utilised, is the primary regulatory determinant in protecting the cell against the injury by its defensive enzymes and metabolites in which glutathione

peroxidase, glutathione reductase, reduced glutathione, and oxidized glutathione are primarily responsible for fighting any oxidative stress created due to glucose toxicity [15,16]. Moreover, the other enzymes also play important roles when an excess of oxidative stress comes under existence in which catalase, superoxide dismutase, GST, etc play the roles to protect the cells [17]. However, it has been observed that the defense system of the tissue is decreased in diabetes due to down-regulation of PPP of the cell [18].



Glycation, Immune and Defense System

A critical analysis of defense and the immune system is needed to be elaborated which can help physicians to treat diabetics in a better way as also compared to cancer cells wherein the immune system of normal cells has been shown to be decreased to fight and dismantle cancer cells. Therefore, the two noble prizes in the names of Dr. Allison and Dr. Honjo in 2018 have been endorsed on immune system enhancement to kill cancer cells. Likewise, in diabetes, the immunity of the cells is decreased and it has to be enhanced so that the body should feel stronger and no

symptoms of diabetic complications should appear physically or internally to ally the normoglycemia for better functioning of cells. The blood glucose levels in diabetics are vulnerable to change drastically without food or having food due to a lack of insulin endeavor. In such a situation glucose becomes the mastermind to glitch the damage. Ironically, it cannot be underestimated the roles of free radicals generation in such fluctuating glucose levels and the beginning of glycation processes [19]. If it prolongs the body feels weak in spite of good control on blood glucose levels and the so called a good glycosylated hemoglobin

percentage. It has been observed in diabetics that they do not feel stronger even having a normal range of fasting and pp glucose [20]. They have also a normal range of glycosylated hemoglobin percentages. Now a question arises what gets improper for their laziness? The answer has to be discovered. But, it is the opinion that there may be hampering of immune and defense systems at micro levels in diabetics which have to be discovered.

Responding to anti-diabetic drugs by different genetic makeup and functionalities of humans, it has been observed that the young diabetics take a minimum dose whereas the old aged diabetics take multiple drugs to maintain normoglycemia [21]. It clears the concept that the defense and immune system in young is stronger even in a disease condition but the old aged faces a weak for the same. Obviously, the physicians do not try on enhancing the defense and immune system in diabetics.

Constipation, Immune and Defense System

Now a better understanding of diabetes and its defense and immune system in the stomach is perceived to be 70% of the cells that make up the

immune system [22], which can be considered and elaborated. The diabetics generally face acute or chronic constipation [23]. Constipation generates toxic gases like hydrogen disulfide, carbon monoxide, methane, etc [24]. The constipated diabetics generally do not take a good meal to quench hungriness due to less appetite and indigestion leading to malfunctioning of liver [25]. It has been reported that constipation causes early neuropathy in the legs of diabetics [26]. It has also been observed that if constipation is well managed, the neuropathy in the legs vanishes or diminishes [27]. Therefore, better management of constipation is the basic need to halt the early development of diabetic constipation.

Liver, Immune, and Defense System

Liver is the main tissue where thousands of biochemical reactions are going on. The complexity arises as the glucose is not being converted to glycogen, what may be the consequences of excess glucose on ongoing liver's biochemical reactions, has been frantically investigated in the past but their abnormal at micro levels are scanty. For better functioning of liver, the blood test of GOT and GPT are being preferred which are concerned to protein

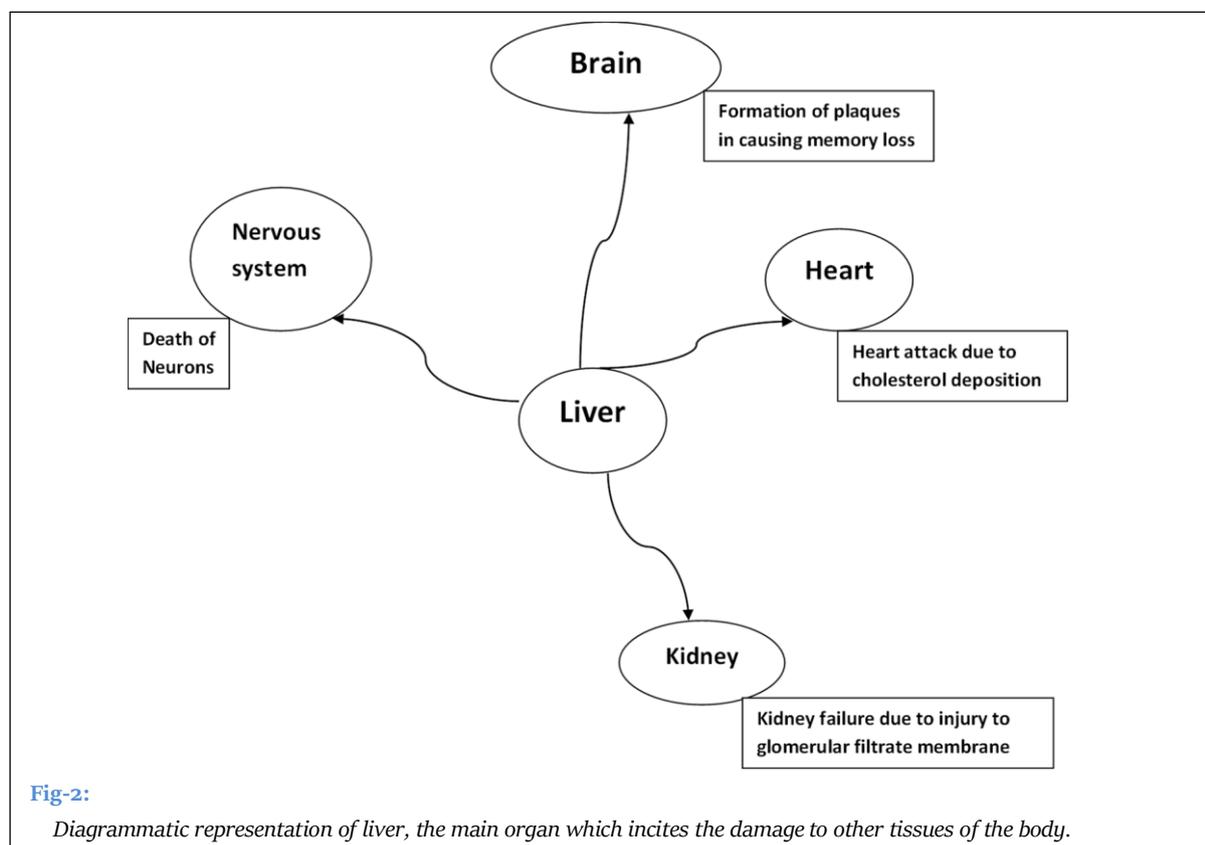


Fig-2:

Diagrammatic representation of liver, the main organ which incites the damage to other tissues of the body.

metabolism [28]. Can it be inferred that the other diseases conditions, GOT and GPT levels proclaim for a healthy liver? Here the diabetes is not a disease but a metabolic disorder, therefore, at micro levels the study of liver damage can be proof for a healthy liver. The other tissues functionaries are totally dependent on liver functions (Fig-2). There is a need of researches on converting glucose into glycogen by modulating the metabolism in liver, the whole drawbacks of excess glucose in the blood will be no more important in diabetes, and when needed the glycogen will be converted into glucose.

Gut Bacteria and Immune System

Moreover, the number of gut bacteria increases in diabetes due to easily available glucose [29]. The excess glucose in the gut lining causes improper functioning of the cells of Cajal, the pace-maker of the intestine [30]. The gut bacteria are the hidden maker of creating a less immune and defense system in diabetics. The increased number of gut bacteria should be minimized by providing a specific diet so that constipation should not be at the expense of diabetes [31].

Drugs, Herbal Drugs, and Immune System

The allopathic drugs have not been innovative to enhance the immune system in diabetics. The role of

antibiotics is ruled out as they are for fighting disease. Generally, the antioxidants are being preferred to enhance the immune and defense system but they are not logically commemorative to pick up the immune and defense system rather than explicit to quench the free radicals to a lesser extent [32]. The excess use of antioxidants like Vit C found in citrus fruits may damage the kidney [33]. There have been several herbal medicines which become the alternative to handle the immune system in diabetics. Their precise roles have to be explained because plenty of enhancers and modulators are present in them [34,35]. It has been observed that turmeric enhances the immune system. Gupta B L et al., (2019) [20] discovered that turmeric along with black pepper keeps normoglycemia in diabetics with a good control on constipation and indigestion with a strong feeling of the body. These herbal duos have been beneficial in transforming the treatment mode from multiple drugs to single-drug therapy. The differential fasting glucose levels and glycosylated hemoglobin have been put as the parameters to determine the different doses of turmeric and black pepper (Table-1). One to thrice doses of these herbal medicines based on age and duration of diabetes have been best suited not only in maintaining the normoglycemia but also for better functioning of the other tissues.

Table-1: Treatment of diabetics with turmeric and black pepper (5:1) 4-5 gm based on FG, PPG and glycosylated haemoglobin (GHb%)

S.N.	Diabetics treatment	FG	PPG	GHb%
	(Turmeric + Black pepper)			
1	Thrice a Day	>200 mg/dl	>300 mg/dl	>10%
2	Twice a Day	150-200 mg/dl	200-300 mg/dl	>8%
3	Once a Day	120-150 mg/dl	150-200 mg/dl	>7%

FG= Fasting Glucose; PPG= Post Prandial Glucose; GHb= Glycosylated Haemoglobin

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Conflict of Interest

All authors have read and approved the final version of the manuscript. The authors have no conflicts of interest to declare.

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