

Glycation Regulation by Fermented Herbal Decoction

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Abstract

Objective: Diabetes mellitus (DM) is a common physical disorder of the senile. Patients with DM are at risk for high mortality with reduced immune capability and abnormal carbohydrate metabolism. Fermented herbal decoction: FHD is an acquired virtual glycoprotein with glycosylation-dependent immunomodulatory activity. We hypothesized that aberrant carbonized metabolism in DM was associated with changes in the glycosylation of FHD, dealing to Specific immuno-adaptive activity.

Research Design and Methods: FHD was purified by affinity chromatography. The structural analysis of protein glycosylation was preformed by lectin-binding assay and mass spectrometry. Cytotoxicity, cell death, cytokine secretion, FHD binding of FHD-administered lymphocytes and natural killer cells (NK) were determined. Sialidase activity of the tissues of normal and DM patients was measured.

Results: FHD affected glycosylation, but not the protein nucleus of FHD. FHD had reduced immuno-suppressive activities related to cytotoxicity on lymphocytes, inhibitory activities on interleukin IL-6 secretion by lymphocytes, stimulating activities on IL-1 secretion by dendritic cells and binding to these cells. Desialylation eliminated the immunomodulation and binding of FHD. Senile with DM-sialidase activity has been increased in life-related diseases, which may be responsible for the reduced silicic acid content of the lymph.

Conclusion: We had reported that FHD; fermented herbal decoction regulated DM by long term administration via regulation of glycation. Although the mechanism of action was not yet clear. The purpose of this study was to investigate the effect of FHD on glycation *in vivo*.

Following were the summary of this results:

1. FHD regulated glycation by long term administration.
2. The glycation was evidenced by circulatory system.
3. The glycation was evidenced by peripheral capillary.
4. Cytokine IL-6 was leveled up after administration of FHD.
5. These results confirmed by experimental animal, muse system.

Keywords: QOL; Finger Movements; Constitution; Complement; Decoction of Fermented Herbs; Intestinal Flora; Intestinal Absorption; Bowl Movement

Abbreviations

CAM: In addition to complementary and alternative medicine and Western medicine, there are other traditional medicine and health promotion menus around the world; DM: Diabetes Mellitus; FHD: Fermented Herb Decoction; G-rich type: Peripheral blood granulocytes account for more than 60% and are more common among young people

Introduction

Nowadays, complementary and alternative medicines (CAM) have spread highly attractive one since they are able to responsible many life-style related diseases, such as DM that spread in the modern world agitated by CONID-19 [1]. The present report had tried to show that typical styles of CAM, preparing special molecule for digestive and easily expanded human complement component that regulates the functions of leukocytes in the human immune system [2-8]. We had been studied and suggested that the health-promoting supplement after down-sizing the polysaccharide to suitable fragment it was possible to activate complement system [9,10]. These activities were specially part of complement pathway, alternative complement pathway. Dietary supplements and FHD proposed as a potent agent dietary supplement for regulating an acquired immunity including the activating alternative complement path.. These methods were a close connection of the complement activation process other than the invasion of microorganisms, where the immune complex and/or toxic polysaccharide such as LPS worked as a way of alternative complement pathway. On the other hand, the immune system works for the local infection of microorganisms, antigen presenting cell throughout the immune system directed to the endocrine and nervous system. In this report, it was suggested that FHD could have a qualitative and quantitative effect on immune-competent cells, thereby activating lymphocytes in the constitutional manner. FHD had been used as a remedy, and the implication was done little on the properties of the leukocyte subset, such as granulocytes and lymphocyte ratio. In this article, we also suggested focusing on identifying the FHD formula, which refers to another herbal medicine that was the first line of CAM. The influence of FHD on its relationship to leukocyte and/or lymphocyte subpopulations was also discussed. The overall mechanism of FHD on the phagocytic cell is also discussed with regard to complement activation of particularly alternative complement path. This phenomenon was only found to prepare chained saccharide, which makes it possible to activate the complement pathway produced by acidophilic bacteria and yeast fungi [10].

Methods

Preparation of pre-fermented 80 and fermented 80

A market available wild herbs were fermented and extracted with appropriate amount of boiled water (98°C) to 10gr and extracted for 30 minutes. The extract was performed by *Lactobacillus leuteri* for 6 months at 30°C and was repeated twice in the method described in M & M. After centrifugation of 2000xg for 10 minutes at normal temperature and served for FHD.

GABA cirtification for fermentation

City-side available wild herbal plants, MANYOH have been prepared by ECHIGO YAKUSOH, Co. Ltd. Niigata, Japan. Fermentation was prepared by *Lactobacillus leuteri* for 6 months at 20°C condition. GABA: Gamma-amino acid-butyric acid was traced through the check system [11].

To prove the fragmentation of the substances FHD, we employed a simple method to study the positive materials fermented by *Lactobacilli* instead of HPLC: high-pressure liquid chromatograph. GABA: γ aminobutyric acid detectable. Was used by the probe of fermentation and degradation. GABA, reduced nicotinamide adenine di nucleotide phosphate using a specific enzyme, aminotransferase and dehydrogenase, which correspond to the steps for the production of reduced nicotinamide adenine di nucleotide phosphate suggesting a specific enzyme, aminotransferase and dehydrogenase, the oxidized nicotinamide adenine-di nucleotide phosphate as a coenzyme and

inactivate the enzymes, thereby producing any amino acid having an certified structure as GABA and acting electron molecule on NADPH, which is followed by production of the mixture of a tetrazole salt that can produce a water-soluble formazan dye is detected and described in references [12].

A physiological process, glycation is a non-enzymatic reaction between free amino groups of proteins and reducing sugars, in a process of initiated by the generation of acid-labile Schiff base adducts that undergo subsequent rearrangement to form FHD products. These early glycation intermediates undergo slow, irreversible and complex transformations and form advanced glycation end products (AGEs) [13]. Once the AGEs are formed, they accumulate continuously on these proteins throughout the biological lifetime. They promote cross-linking of amino groups to each other and cause aggregates of proteins, especially collagen. AGEs have been identified not only in long-lived proteins but also in short-lived proteins such as plasma proteins [14]. AGEs bind to specific macrophages and other cells through AGE receptors and are strongly implicated in the initiation and acceleration of organ damage [3]. The generation of AGEs is accelerated during hyper-glycaemia. Accelerated cumulative modification of proteins and other biomolecules contribute to diabetic complications involving multiple organ damage, including vasculature, lens, kidney and nerves [15]. Amino-guanidine (AG), which blocks AGE formation by interacting with fragmentation products, was found to be useful in preventing experimental diabetic nephropathy and retinopathy [16] and is used as a standard compound for protein glycation inhibition studies. Carnitine (CA, β -hydroxy- β -trimethylamino butyrate) is a ubiquitous constituent of mammalian plasma and tissues, mainly distributed among skeletal and cardiac muscles. CA is supplied to the body through dietary sources such as meat and dairy products and is also biosynthesized from lysine and methionine. CA has effects on fat and glucose metabolism. The cellular function of CA is to bind to free fatty acids and to regulate their transport into mitochondria for β -oxidation [16]. Thus CA can promote oxidative metabolism of glucose through its effect on pyruvate dehydrogenase enzyme complexes. Deficiency of plasma total and free CA levels has been observed in type 2 diabetic patients and is related to specific diabetic complications [17]. Previously we have shown that CA could improve insulin action and reduce oxidative stress in fructose-fed rat model of insulin resistance [18]. Consequently, the purpose of the present study is to explore the preventive effect of CA on glycation in fructose-fed rats and on *in vitro* glycation and AGE formation with bovine serum albumin (BSA) as the model protein. We also studied the effect of CA in regeneration of glucose use by control rat membrane compared to insulin.

The placental changes and an increased risk of diabetes in the mother and offspring later in life [19]. The underlying pathophysiology of DM has been associated with disorder of immune responses, such as changes in immune cell subpopulations and cytokine production in women with DM [20].

Glycosylation is definite for the normal physiological activities of glycogen [21]. Its significance is proved in the lack of immunomodulatory activity in two other glycodelin isoforms with different glycosylation, glycodelin-S and glycodelin-C [22]. Although there is no difference in the glycodelin concentration of the serum of patient in the first trimester [23] and the [24] Hyper glycaemia in diabetes causes abnormal carbohydrate metabolism and the production of advanced glycation end products, leading to a change in gene expression and the activities of cellular glycosyl transferases and glycemic diseases [25]. Diabetic has been associated with changes in glycosylation and subsequently with the biological activities of human chorionic gonadotrophin [26] and placental transferrin receptor [27]. However, due to the lack of advanced methodological methods, these studies did not provide detailed information on glycan structures and the resulting changes in biological activities.

Prevention of disease is very important in the planning of treatment. To this purpose, it is important to look at the constitution from the prevention side, especially for the allergic reaction. The purpose of this report is to introduce the CAM menu, which can change the composition by some menus of CAM with moderate regulation. Abo reported that the subsets for white blood cells and the lymphocyte granulocyte ratios in each individual is very important [28]. Then the purpose of this report is also to show the importance of stressing the digital word in order to clarify the state of any physiological disease even in allergic condition.

Choosing the health menu associated with any constitution is important because there is a lack of information about these interactions between the public and health professionals, leading to absolute important health standards. In other words, there is still no interim measure to assess the degree of concentration of each study. Therefore, we report on the best candidates for the digital expression of the lymphocyte granulocyte ratio and the results of the regulatory vector expressed as linear function [29], such in CAM therapy. With these respects, we reported that the immune system was closely related to the QOL in individuals, which is associated with leukocytes in quantitative and qualitative [30].

Research Design and Methods

Normal and diabetic amniotic fluid samples. The present study protocol was established by the Institutional Review Board of the University of Hong Kong/Hospital Authority. A total of blood samples (20 normal and 15 DM) were collected from women. The diagnosis DM was made according to the criteria of the World Health Organization with a 2-h 75g oral glucose tolerance test (OGTT) [29]. Blood glucose levels 7.8 mmol/L were defined as having DM. Two groups of volunteer with DM were treated with insulin and 13 women with DM were treated through diet control. The demographic information on the participants of mothers and young children of normal and DM participants is shown. The two groups of women were similar in gravity, party, age, BMI, pregnancy age at birth, fasting plasma glucose and placental weight and fetal birth weight and differed only in 2-h plasma glucose. The amount of isolated from each amniotic fluid sample was limited. Therefore, the sample was randomly pooled into two groups for experimentation.

PMBCs, junket (T-lymphoma cells) and OE-E6/E7 (oviductal cell line) were cultured in RPMI-1640 medium (Sigma-Aldrich). TEV-1 (trophoblast cell line) was cultivated in the DMEM medium (Sigma-Aldrich). All cultural media were supplemented with 10% FBS.

Determination of the glycodelin concentration in amniotic fluid. The glycodelin content from the amniotic fluid of normal and DM pregnancies was determined by enzyme-bound immunosorbent assay (ELISA). Polyclonal goat of antihuman glycodelin antibodies (1 mg in 100 mL; R&D systems, Minneapolis, MN)- coated assay wells were successively incubated with the amniotic fluid sample.

Concentrations of glucose, fructose and fructosamine in plasma and glycated hemoglobin and methylglyoxal in the blood were significantly higher in fructose-fed animals than in control rats.

Administration of CA P. Rajasekar, C.V. Anuradha: L-Carnitine inhibits protein glycation 85.

The incubation medium contained 0.04M sodium phosphate (pH 7.2), 0.005M potassium chloride, 0.004M magnesium chloride, 0.006M glucose and 0.08M sodium chloride. *Compared with CON; #compared with INS; significant at $p < 0.05$ (Student's t-test) values are mean \pm SD of 6 experiments Fluorescence (AU) Percentage, % 120 Inhibition %.

Glycation caused a significant increase ($p < 0.001$) in glucose utilization (CA 1 mM and CA 2 mM) as compared with untreated control. When the hemi-diaphragms were incubated with CA in the presence of insulin (0.2 U/ml), it was seen that there was a significantly ($p < 0.001$) larger effect than when both were present alone. Hence the effects of insulin and CA on glucose metabolism by the diaphragm are additive. Glucose disposal by diaphragm was followed over time and the results are reported in figure 3. CA at both concentrations (1 and 2 mM) caused a significant increase in glucose disposal as compared to control. CA exerted a stimulatory effect during the subsequent period of incubation. Thus CA was capable of maintaining the ability of the tissue to metabolize glucose. In the presence of both CA and insulin the utilization of glucose was greater than when they were present alone.

Results

Serum level

The process is initiated by the generation of acid-labile Schiff base adducts that undergo subsequent rearrangement to form stable Amadori or Heyns products. These early glycation intermediates undergo slow, irreversible and complex transformations and form advanced glycation end products (AGEs). Once the AGEs are formed, they accumulate continuously on these proteins throughout the biological lifetime. The level of AGE in senile (ave. was 74.6 yo) higher than the younger group (ave. 40.2 yo). After administration of FHD, both groups down regulated, but drastic change was seen in younger than that of younger group (Figure 1).

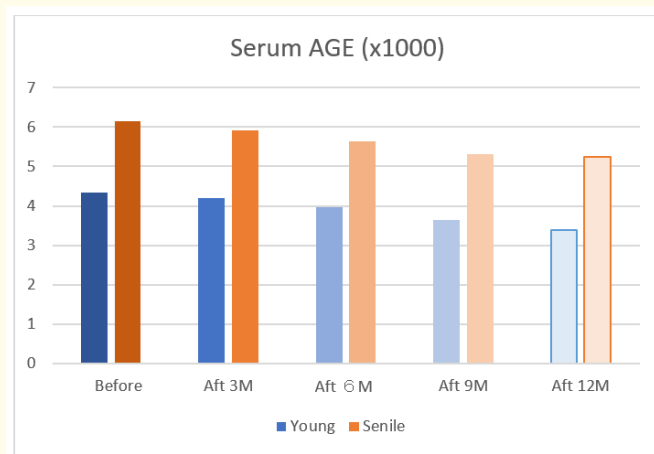


Figure 1: Serum age (x1000).

Age level in peripheral capillary

These early glycation intermediates undergo slow, irreversible and complex transformations and form advanced glycation end products (AGEs). Once the AGEs are formed, they accumulate continuously on these proteins throughout the biological lifetime. The final trial to show the fatigue of the volunteers, the index FF/GAPDH was selected as a maker of glycation. After start to compare, the level of younger group was clearly low, indicating they are vital compared than the senile. After administrating FHD, both groups were downregulated according to the time factor. The pattern in both group was different. The younger group showed clear decedent in factor. However, senile one was not so clear decedent than the younger group (Figure 2).

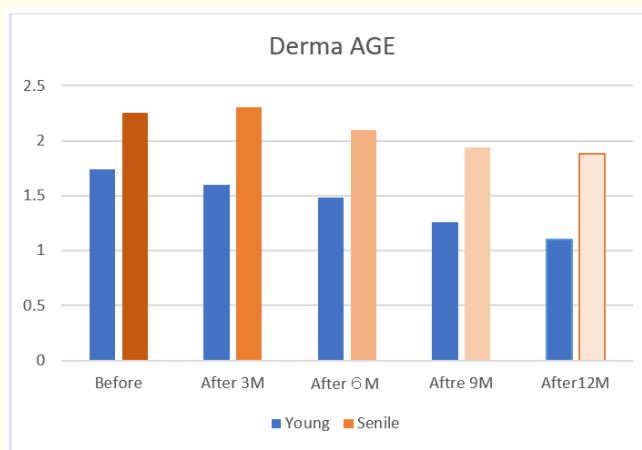


Figure 2: Derma age.

IL- 6 level in serum

These early glycation intermediates undergo slow, irreversible and complex transformations and form advanced glycation end products (AGEs). Once the AGEs are formed, they accumulate continuously on these proteins throughout the biological lifetime. We tried to select cytokine IL-6, as another marker of glycation [31].

After informed consented to the volunteer, we tried to compared the cytokine IL-6 in the peripheral blood. For this marker, the serum level in senile (ave was 74.6 yo) higher than the younger group (ave 40.2 yo) also. After administrated both senile and younger group, the both group were the same trend of small change after (Figure 3).

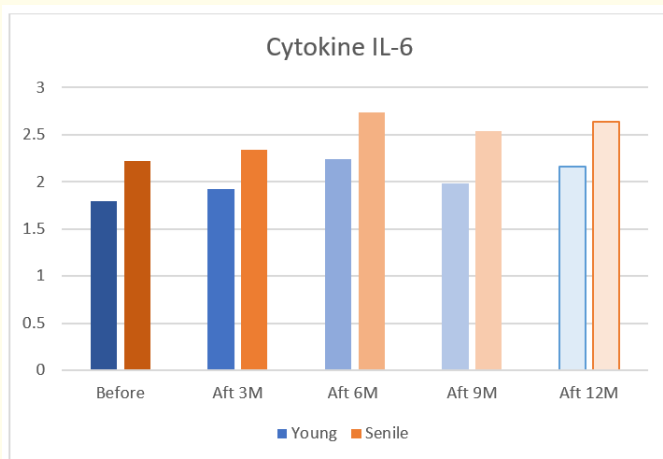


Figure 3: Cytokine IL-6.

Experimental mice system

In human system, individual defenses are very high, age, sex, life-style etc.

DDY white mice were prepared and induced experimentally induced diabetes mellitus (DM) by injecting STZ; streptozotocin.

Mice were prepared into two groups, one is control group and the other was experimental groups. The experimental groups were further divided 5% of FHD and other was 20% of FHD.

As a results, experimental groups were increased the percent of glycation according to the time after, 3 days and 7 days.

The results were dose dependent and time dependent manner (Figure 4).

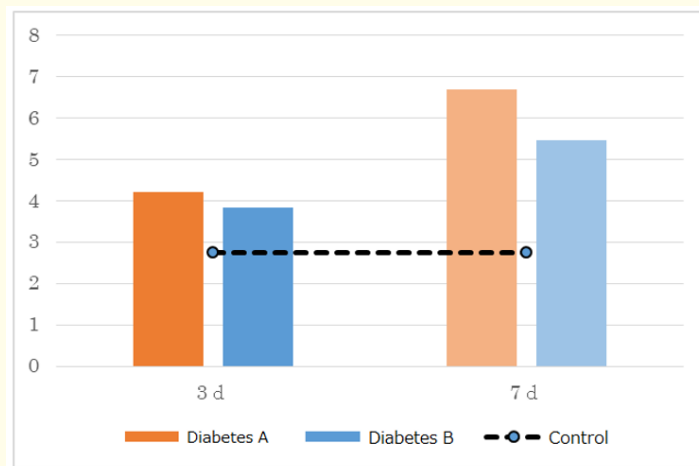


Figure 4

Discussion

Altered glycosylation of glycoproteins and glycolipids suggested in diabetes, cancer, AIDS, Alzheimer's disease and inflammatory diseases such as high leveled group of tissue degradation, PCD [32]. Two observations in this study show for the primary changes in the glycosylation of FHD in DM. First, binding affinities to ConA and WGA were lower than FHD's. Second, glycol analyses of N-glycines revealed significant quantitative and qualitative differences in glycel-glycan structures between FHD. The most important quantitative difference is the smaller amount of 2-6 sialylated glycans in FHD. An interesting qualitative difference is that most of the sialylized glycans in FHD.

Sialic acid amount on glycoproteins are controlled by sialyl transferases during their cellular metabolism and in some incidence by sialidase(s) producing cells. Decreases in sialyl transferase [33] and increase in sialidase activities [34] as well as regulation in other glycosidase activities [35] have been reported in humans and animals with diabetes. These reports correspond to the increased free silicic acid amounts in the serum of type 2 diabetes [36]. Human endometrial tissue produce both sialidase and sialyl-transferase [37]. In this paper, triclidase activity in DM is higher than in normal one, in line with the reported abnormal carbohydrate metabolism in the deviance unit of DM [38].

Sialic acid is the end products monosaccharide in human N-glycans, and it affects the conformation, binding, and biological activities of glycoproteins [39]. The relative amount of some silicic acid-containing glycoproteins in sample fluid [40] and maternal blood cell is increased during pregnancy and increases with progressive manner. In fact, the absence of silicic acid in various glycodelin isoforms correlates with its apopto-inducing activity on lymphocytes [41]. Consequently, FHD with less sialylized substance has reduced the apopto-inducing activity to lymphocytes, underscoring the importance of sialic acid in the mediation of the immunomodulatory function of FHD.

In such a condition, the selective deletion of T-cells occurs at the feto-mother interface throughout the pregnancy [42]. Suppression of the reaction of maternal lymphocytes to fetal alloantigen is necessary for fetal survival [43]. FHD modulates the T-cell population by inducing apoptosis of T cells and expression in Th-1 lymphocytes [44]. The decreased ability of FHD to induce T-cell apoptosis could be at least partly responsible for the increased lymphocytes served in DM patients. The involvement of carbohydrate metabolism in the change in the T-cell population in DM is reflected in the reduction of T cells after insulin treatment of these women [45].

Changes in FHD glycosylation can also lead to in suitable cytokine profiles in DM. A shift in the cytokine profile in women with DM has been reported [46,47]. Whether this is related to an increased risk of complication in DM suggest to be proof. Significantly, T cells treated with FHD produce more IL-2 than FHD-treated cells. The production of Th-1 cytokines including IL-6 would lead to the rejection of semi-allographs such as organ transplantation. On the other hand FHD has Impaired stimulatory effect on IL-6 secretion by NK cells. IL-6 has a wide range of biological activities, including stimulation of trophoblast invasion and hCG production [48,49].

The FHD have impaired binding affinities to lymphocytes and NK cells. Silicic acid receptors, such as silicic acid-binding immunoglobulin-like lectin receptor, on leukocytes have been proved to mediate the effect of glycodelin, also carry the epitopes, but only the former has immunomodulatory activity. Second, another glycodelin isoform, glycodelin, contains more high mannose glycans than FHD, but glycodelin-S is not immuno-suppressive [50,51].

It is possible that the changes in FHD glycosylation in DM are related to increased placental cancer activity and therefore not applicable to all types of diabetes. It also remains to be seen whether the changes described here have any compounds with fetal complications or have clinical consequences of altered immune cell reactivity. In type 2 diabetes, an increase in serum silicic acid levels is an indication of the loss of sialylation due to circulatory and membrane glycoproteins. in approaches to correcting the glycosylation changes can help alleviate some of the complications associated with DM. In this context, it has been shown that the glycosidase inhibitor miglitol for the treatment of type 2 diabetes changes the NN-linked glycemic coziness of secretory glycoproteins [50].

Conclusion

From this trial, FHD; fermented herbal decoction gave us following conclusions:

1. The glycation regulation was proved by more than 3 months administration of FHD.
2. The glycation was evidenced by circulatory system.
3. The glycation was evidenced by peripheral capillary.
4. Cytokine IL-6 was leveled up after administration of FHD.
5. The same result was evident by animal system, mice.

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