SYNOPSIS

Synopsis of the Ph.D. thesis on

Evaluation of Adipokine Gene Polymorphisms in Type 2 Diabetes and Therapeutic Potential of GABA and Caloric Restriction in Type 2 Diabetes Mouse Model

To be submitted to

The Maharaja Sayajirao University of Baroda, Vadodara

The Department of Biochemistry,
The Maharaja Sayajirao University of Baroda.

For the degree of

Doctor of Philosophy in Biochemistry

By

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Introduction

Diabetes Mellitus (DM) is a metabolic disorder characterized by persistent hyperglycaemia. The number of individuals with diabetes has continued to grow over the years. It is mainly classified as type 1 diabetes (T1D) and type 2 diabetes (T2D). T1D (less than 10%) is triggered by autoimmune-mediated destruction of pancreatic β-cells. On the contrary, T2D accounts for over 90% of diabetes patients and is manifested by insulin resistance in peripheral tissues due to impaired insulin signalling cascade. Both forms of diabetes are associated with secondary complications that affect multiple organs (1). T2D is caused by a combination of genetic and lifestyle factors such as diet, obesity, lack of exercise and ER stress. Adipose tissue (AT) is an energy storage organ that secretes bioactive molecules called adipokines (pro and anti-inflammatory). The pro- and anti-inflammatory adipokines such as resistin, omentin-1 and vaspin are in a state of equilibrium and they play an important role in regulating metabolism, insulin sensitivity and satiety. The pharmacological interventions for T2D involve two methods: i) insulin secretion from β-cells and ii) insulin-mediated glucose uptake from peripheral tissues (1). The existing therapies only help improve hyperglycaemia and other symptomatic characteristics. Since control of glucose levels can thwart the devastating complications of diabetes, research now focuses on β-cell regenerative therapy.

I. Resistin

Resistin, a pro-inflammatory adipokine, located on chromosome 19p13.2 is secreted by macrophages that infiltrate adipose tissue (1). Increased resistin levels are shown to inhibit insulin signalling pathway. The putative role of resistin in the pathogenesis of human obesity and diabetes led to genetic studies in different populations (2). Single nucleotide polymorphisms (SNPs) in the promoter region of resistin gene have been shown to increase T2D susceptibility by elevating circulating resistin levels (1, 2). The promoter polymorphisms of resistin are also associated with non-alcoholic fatty liver disease (NAFLD), coronary artery disease (CAD) and polycystic ovarian syndrome (2).

II. Omentin-1

Omentin-1, the anti-inflammatory adipokine gene, is located on chromosome 1q22-q23 and is secreted by visceral adipose tissue (VAT) (1). Omentin-1 has been implicated in the insulin signalling pathway by Akt activation and consequently increasing insulin sensitivity. Reports suggest that reduced Omentin-1 gene expression and circulating plasma omentin-1 concentrations are associated with impaired glucose tolerance in T2D patients (1). There are a

few studies on the genetic variants of omentin-1 where Val109Asp rs2274907 has been exclusively studied for NAFLD, CAD, breast cancer and rheumatoid arthritis (3). There is only one report on omentin-1 SNP, 3'UTR rs1333062 in the Indian population showing an association with diabetes (3).

III. Vaspin

Vaspin, a member of serpinA12, was initially discovered in VAT of Otsuka Long-Evans Tokushima fatty rat (1). It is an anti-inflammatory adipokine reported to inhibit kallikrein 7 (a serine protease that degrades insulin). It promotes cell proliferation, inhibits apoptosis and ameliorates ER stress *in-vitro* (1, 4). Vaspin is located on chromosome 14q32.13. SNPs of vaspin are well explored, especially intronic polymorphic sites (intron 2 rs77060950 G/T and intron 4 rs2236242 A/T) were investigated for their association with various diseases like T2D, metabolic syndrome, CAD, NAFLD, and obesity (4).

III. Calorie restriction (CR)

Dietary intervention has long been considered as a first-line therapy for diabetes management by researchers and clinicians around the globe. CR, a dietary intervention, is described as a reduction in caloric intake typically by 20–40% of ad libitum consumption, whereas sufficient intake of protein and micronutrients are maintained at levels sufficient to avoid malnutrition (5). CR attenuates the degree of oxidative stress and increases the transcript levels of genes involved in mitochondrial function and biogenesis, improves insulin sensitivity, fasting blood glucose (FBG), other cardiometabolic risk factors (hypertension, dysglycemia, dyslipidemia, abdominal obesity and insulin resistance) and reduces pro-inflammatory adipokines and total cholesterol (6).

IV. γ-Aminobutyric acid (GABA)

GABA has emerged as a new anti-diabetic dietary supplement. GABA, a major inhibitory neurotransmitter has proven a role in islet-cell hormone homeostasis, preservation of the β-cell mass, suppressing detrimental immune reactions and apoptosis (7, 8). GABA generally regulates cytokine secretion from human PBMCs and suppresses β-cell-reactive CD8+ CTLs in T1D mouse models (7, 8). The encouraging reports of GABA on T1D led to studies on T2D mouse models as well. The activation of GABAA-Rs and GABAB-Rs receptors (GABA receptors on β-cell) can induce β-cell replication and activation of α-cell GABAA-Rs can promote their conversion into β-cells (7, 8). GABA has been reported to promote human β-

cell replication and islet cell survival in *in-vivo* and humanized mice (7, 8) by up-regulation of Pdx-1 expression.

Hypothesis

From the above, we hypothesize that the genetic variants of resistin, omentin-1 and vaspin with their altered levels may play a role in the development of obesity-induced T2D in human population. It is further hypothesized that combination effect of CR and GABA in the T2D mouse model would ameliorate the T2D pathophysiology in a synergistic / additive manner.

Significance of the study

Our population study would be helpful to uncover the underlying mechanism behind the involvement of adipokines in T2D and the development of potential biomarkers for the prognosis of T2D. Our *in-vivo* study in the T2D experimental mouse model would help in elucidating the combination effect of CR and GABA as an alternative therapy for β-cell regeneration and management of T2D pathophysiology.

Proposed Objectives:

Objective I: To study the role of Resistin in T2D.

a. To study association of the following *resistin* polymorphisms with T2D in Gujarat population i) -420 C/G (rs1862513) ii) -358 G/A (rs3219175) iii) -638 C/G (rs34861192).

b. To assess plasma resistin protein levels.

c. To perform a possible genotype-phenotype correlation analysis.

Objective II: To study the role of Omentin-1 in T2D.

a. To study association of the following *omentin-1* polymorphisms with T2D in Gujarat population. i) Intron 1 G/T (rs1333062) ii) Exon 4 Val109Asp (rs2274907)

b. To assess plasma omentin-1 protein levels and *omentin-1* transcript levels in adipose tissue.

c. To perform a possible genotype-phenotype correlation analysis.

Objective III: To study the role of Vaspin in T2D.

a. To study association of the following *vaspin* polymorphisms with T2D in Gujarat population. i) Intron 1 A/G (rs76624128) ii) Intron 2 G/T (rs77060950)

b. To assess plasma vaspin protein levels and *vaspin* transcript levels in adipose tissue.

c. To perform a possible genotype-phenotype correlation analysis.

Objective IV: To investigate the effect of Calorie Restriction (CR), γ-Aminobutyric acid (GABA) and combination treatment on pancreatic β-cell proliferation in High-Fat Diet (HFD) + Streptozotocin (STZ) induced experimental mouse model.

a. To establish HFD + STZ induced T2D mouse model.

b. To assess glucose tolerance and insulin sensitivity.

c. To estimate plasma insulin and lipid profile.

d. To study transcript levels of glucoregulatory enzymes in the liver; lipid metabolism enzymes in the adipose tissue and mitochondrial biogenesis markers in the skeletal muscle.

e. To study mitochondrial respiration in the skeletal muscle.

f. To assess β-cells regeneration and apoptosis in the pancreas.

Results:

Objective I: To study the role of resistin in T2D.

We recruited age, sex and ethnically matched 502 controls (252 males and 250 females) and 469 T2D patients (253 males and 216 females) from Gujarat, India. The patients showing FBG >125mg/dl and controls exhibiting FBG <110 mg/dl with no prior history of T2D were included in the study. Ethnically and geographically matched individuals were randomly selected from Gujarat through community screening program. The height and weight of the study participants were measured to calculate BMI. Participants were subjected to overnight (12 h) fasting and their venous blood samples (3ml) were drawn to estimate Fasting Blood Glucose (FBG), Lipid profile [Total Cholesterol (TC), Triglycerides (TG), Low-Density Lipoprotein (LDL) and High-Density Lipoprotein (HDL)], and resistin from plasma. Genotyping was carried out from the genomic DNA extracted from PBMCs. Genotyping was done by Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP) for rs34861192 G/A, rs1862513 C/G and rs3219175 G/A. For the genotype-phenotype correlation analysis metabolic and plasma lipid profile were used. Plasma levels of resistin were assayed by ELISA.

Clinical parameters differed significantly between controls and patients. Patients had significantly higher FBG levels ($p<0.0001$), BMI ($p<0.0001$) and TG ($p<0.0001$) while, HDL was significantly decreased in patients (males: $p=0.0037$, females: $p<0.0001$). The distribution of genotype frequencies for all the polymorphisms was consistent with Hardy-Weinberg expectations in both patient and control groups ($p>0.025$). rs1862513 C/G was found to be significantly associated with T2D individuals (genotype and allele frequencies, $p<0.0001$). rs34861192 G/A was found to be monomorphic in controls and T2D patients and

rs3219175 G/A was not found to be associated with T2D. Thus, the genotyping for the above-mentioned SNPs were discontinued after the initial assessment. A haplotype evaluation of the two polymorphisms did not differ significantly. CC genotype of rs1862513 C/G has been found to be associated with increased FBG (p=0.0035), BMI (p=0.0004) and TC levels (p=0.0190). Plasma resistin levels were monitored in 40 controls and 40 patients and a significant increase (p=0.0129) was observed in T2D patients. Our findings suggest rs1862513 C/G polymorphism of *resistin* as an important factor which could pose a risk towards T2D susceptibility.

Objective II: To study the role of omentin-1 in T2D.

The study protocol was designed as mentioned in the objective I. *Omentin-1* polymorphisms (rs2274907 and rs1333062) were genotyped by PCR-RFLP. Samples of visceral (omental) adipose tissue were taken from the individuals undergoing bariatric surgery. Total RNA was isolated from VAT by Trizol method. The expression of *Omentin-1* and *GAPDH* transcripts was monitored by Real-time PCR. None of the polymorphisms of *Omentin-1* were found to be associated with T2D (p>0.05), and hence, the genotyping was discontinued after an initial assessment of 250 samples. The estimated frequencies of the haplotypes obtained for rs2274907 A/T and rs1333062 G/T did not differ significantly between patients and controls (global p=0.853). *Omentin-1* rs2274907 AT genotype was found to be associated with increased BMI (p=0.0247). Significantly increased *Omentin-1* transcript levels were observed in T2D patients as compared to controls (p<0.0127). Plasma omentin-1 levels showed a significant decrease (p<0.0001) in T2D patients. Our findings suggest that decreased circulatory omentin-1 levels could pose a risk towards T2D susceptibility.

Objective III: To study the role of vaspin in T2D.

The study protocol was designed as mentioned in the objective I. PCR-RFLP and Amplification Refractory Mutation System-Polymerase Chain Reaction (ARMS-PCR) were used for genotyping of *vaspin* polymorphisms (rs77060950 G/T and rs2236242 A/T). Our results showed significant association of i) rs2236242 A/T with T2D (p<0.0001) as the TT genotype conferred 3.087-fold increased risk. ii) Further, rs2236242 TT genotype was associated with increased FBG (p=0.0001), BMI (p=0.0001) and TG levels (p=0.0065). iii) GA (p=0.0053), GT (p=2.46x10^{-6}) and TA (p=0.0441) haplotypes were associated with T2D risk. iv) Vaspin transcript levels (p=0.028) and protein levels (p=0.0001) were significantly decreased in T2D patients and were negatively correlated with BMI (p=0.0307) and FBG (p=0.0006). In conclusion, rs2274907 A/T polymorphism is strongly associated with reduced

vaspin transcript and protein levels, and related metabolic alterations that may play a role in the advancement of T2D.

Objective IV: To investigate the effect of CR, GABA and combination treatment on pancreatic β-cell proliferation in HFD + STZ induced experimental mouse model.

The aim of the study was to evaluate the therapeutic potential of GABA and CR in HFD+STZ induced T2D mouse model. Male C57BL/6J mice (9-10 weeks old) were used in this study. Control group (n=8) was fed with normal chow diet. Mice (n=32) were fed with HFD for 18-20 weeks followed by three low consecutive doses of STZ (40 mg/kg bw i.p.) to induce β-cell loss. Body Weight (BW) and FBG levels were monitored weekly. HFD+STZ induced T2D was confirmed with BW ≥30 grams and FBG ≥350 mg/dL. These animals were then divided randomly into four groups (5 mice/group): 1) Diabetic control (HFD+STZ) 2) CR diet fed (30% reduction of HFD) 3) GABA treated (2.5 mg/kg bw i.p) and 4) CR+GABA treated. Treatment was given daily for 5 weeks along with BrdU on alternative days (100 mg/kg bw i.p.) to assess β-cell proliferation. CR+GABA group improved lipid profile ($p<0.01$), insulin responsiveness and reduced FBG levels ($p<0.001$) as indicated by increased insulin levels ($p<0.01$), insulin sensitivity ($p<0.01$) and glucose tolerance ($p<0.01$). The oxygen consumption rate of mitochondrial complexes (I - III) was measured in skeletal muscle using the Oxytherm Clark-type oxygen electrode. The oxygen consumption rate was significantly increased in complex I, II and III for CR+GABA group ($p<0.05$) as compared to HF+STZ group. It indicated an effect of CR on mitochondrial complex activity by lowering ROS generation. The liver, adipose tissue and skeletal muscle were harvested and stored in RNAlater for the gene expression studies. The transcript expression profile indicates significantly decreased gluconeogenesis (*G6Pase, PEPCK*) ($p<0.05$), glycogenesis (*GLUT2*) ($p<0.01$) and glycogenolysis (*Glycogen Phosphorylase*) ($p<0.05$) and increased glycolysis (*GCK*) ($p<0.01$). Interestingly, lipogenesis was up-regulated indicated by the increased *ACC-1* expression ($p<0.05$). Consequently, as a compensatory mechanism, lipolysis was up-regulated as indicated by an increased *ATGL* expression ($p<0.05$). CR+GABA treatment showed increased *PGC-1α, SIRT-1* and *TFAM* (mitochondrial biogenesis) transcript levels in the skeletal muscle ($p<0.01$). Immunohistochemistry was done on pancreatic tissue sections to assess β-cell regeneration and apoptosis. The percentage of BrdU-insulin co-positive and PDX1-Ngn3-insulin co-positive β-cells was significantly higher in CR+GABA group ($p<0.01$; $p<0.001$) than monotherapy treated groups and HFD+STZ group. Also, CR+GABA group showed a significant reduction in TUNEL-insulin co-positive cells as compared to

HFD+STZ group (p<0.01). However, we did not observe significant apoptosis inducing factor (AIF) translocation in any of the groups suggesting absence of caspase-independent cell death. Thus, CR+GABA improved T2D by increasing insulin sensitivity, glucose tolerance, mitochondrial biogenesis and its complex activities, enhanced transcript levels for key metabolic pathways, increased β-cell proliferation and neogenesis along with reduction in β-cell apoptosis (Figure 1).

Conclusion:

Our population-based findings suggest rs1862513 C/G polymorphism in *resistin* and rs2274907 A/T polymorphism in *vaspin* could pose a risk towards T2D susceptibility. Our findings also suggest that increased plasma resistin levels along with decreased plasma omentin-1 and vaspin levels, with the related metabolic alterations might play a role in the development of T2D in Gujarat population. In addition, CR+GABA treatment ameliorates HFD+STZ induced T2D in mouse model by inducing β-cell regeneration, improving glucose and lipid metabolism and increasing insulin sensitivity in the peripheral tissues**.**

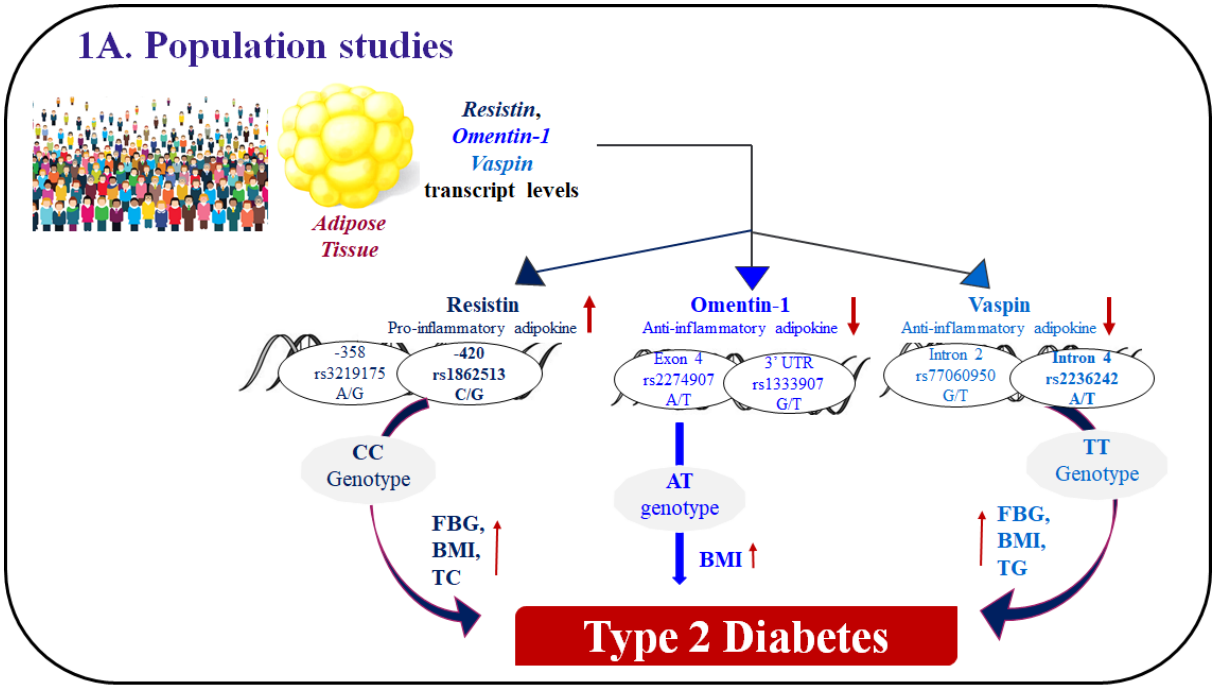

Figure 1A. Role of resistin, omentin-1 and vaspin in development of T2D in Gujarat population. *Resistin* rs1862513 C/G polymorphism is strongly associated with elevated resistin levels and increased BMI, FBG and TC levels. *Omentin-1* genetic variants are not associated with T2D but reduced protein levels indicated a role in T2D susceptibility. Interestingly, *vaspin* rs2274907 A/T polymorphism is strongly associated with its reduced transcript and protein levels, and related metabolic alterations that may play a role in the advancement of T2D.

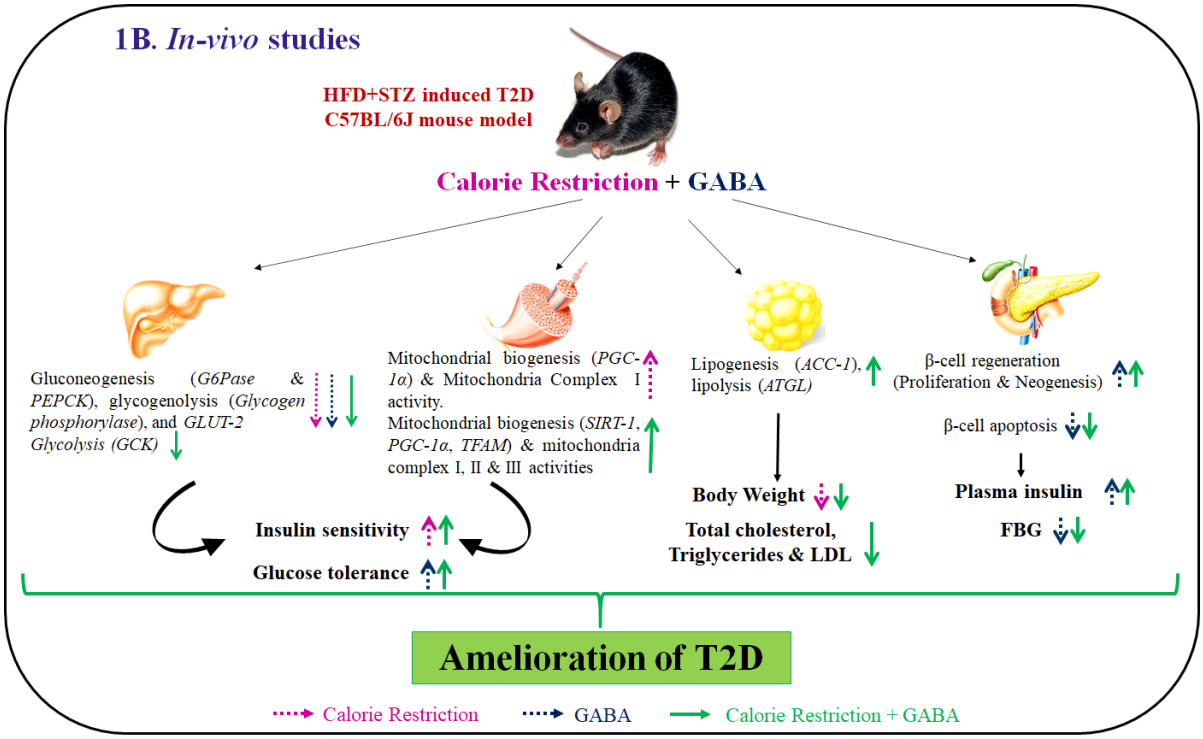

Figure 1B. The combination effect of CR+GABA on amelioration of T2D pathophysiology in the T2D experimental mouse model. T2D pathophysiology is characterized by insulin resistance and β-cell loss. We have evaluated the combination of CR and GABA to induce β-cell proliferation and glucose homeostasis by increasing insulin sensitivity, glucose tolerance, improved key metabolic markers transcript levels, mitochondrial biogenesis and complex activities, and reduced β-cell apoptosis.

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Award:

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Manuscript under preparation:

Calorie Restriction in Combination with GABA Ameliorates Type 2 Diabetes

Posters presented & conferences attended during Ph.D.:

1. **Rathwa N**, Patel R, Pramanik S, Parmar N, Ramachandran AV, Begum R. "GABA in combination with CR as possible therapeutic approach for ameliorating insulin resistance and favoring β-cell regeneration in Type 2 Diabetes" at 9th International Conference on 'Nextgen genomics, biology, bioinformatics and technologies (NGBT) held at Mumbai, India on 30th September- 2nd October, 2019.
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