Adrenergic Receptor Beta 2and 3 Polymorphism Modulate Gastro Intestinal Motility in Ttype 2 Diabetes Mellitus Patients

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Research Article

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Abstract

Background

Individuals with type 2diabetes mellitus (T2DM) commonly present with gastro intestinal symptoms. Exact pathophysiology behind these symptoms is not elucidated. Previous studies reported the role of adrenoceptors on gut motility. However, no study has been conducted to observe whether adrenergic beta receptor (ADRB) 2 and 3 gene polymorphism could influence the gut motility in T2DM.

Materials and Methods:

Three hundred T2DM patients and 200 age and sex matched healthy controls were enrolled for this study. Participants were subjected to lactulose hydrogen breath test for estimation of orocecal transit time (OCTT). To carry out polymorphism study, buffy coat of EDTA blood was used for DNA isolation followed by polymerase chain reaction and restriction fragment length polymorphism.

Results:

In this study, the frequency of C allele as well as CC genotype of ADRB3 gene polymorphism and A allele as well as AA genotype of ADRB2 gene polymorphism were significantly higher in patients than controls and was associated with increased risk for T2DM. On comparison of gut motility, OCTT was found to be significantly prolonged ($p<0.01$) in individuals with CC genotype compared to TT or CT genotype in ADRB3 polymorphism and AA genotype, compared to AG and GG genotype in case of ADRB2 polymorphism. Combined effect of both adrenoceptors on gut motility revealed that individuals having AG or AA genotype in combination with other genotypes had significantly prolonged OCTT.

Conclusion:

It could be concluded that beta adrenoceptor gene polymorphism has significant role on regulation of gut motility in T2DM.

Introduction:

Gastrointestinal symptoms often remain neglected in individuals with diabetes mellitus (DM) resulting in increased morbidity and poor quality of life. These varied symptoms such as dyspepsia, constipation, diarrhoea, are more prevalent in diabetic individuals compared to individuals without DM[1]. However, the association between these gastrointestinal (GI) symptoms and the disorders of gut motility is not elucidated properly. The importance of adrenergic beta 3 receptors on gastro intestinal motility has already been documented.[2] De Ponti and co-workers documented in a review article that adrenoceptors are located in various parts of the gut and modulators of these adrenoceptors could regulate the gut motility[3].

Adrenergic receptor beta 2 (ADRB2) gene located on chromosome 5 having nine polymorphisms. Out of nine, three polymorphisms appear to alter the functional properties of receptor (c.46G.A (pGly16Arg), and c.79G.C (pGln27Glu), as well as c491C.T (pThr164Ile)[4]

Very few studies have reported the association between ADRB2 gene polymorphism and type 2 diabetes mellitus (T2DM) and some of them have contradictory findings. Gjesing et al 2007 [5] showed that Arg16Gly variant had weak association with T2DM while Gly/Gly genotype was primarily present in control subjects. Homozygous carriers of the Arg16 allele of ADRB2 gene had greater risk of hypertension in Swedish subjects with T2DM[6] whereas in Taiwanese population [7] homozygosity of Arg 16 in ADRB2 gene was associated with higher frequency of development of T2DM. Likewise observations by other authors [8] recommended that the amino terminal polymorphisms of ADRB2 gene could be involved in molecular pathogenesis of obesity and hypertriglyceridemia and thus making the person prone to the development of diabetes mellitus. On the contrary, in Korean populations the genetic variability in the ADRB2 gene may not be a major determinant of the development of obesity and DM.[9]

Adrenergic receptor beta 3 (ADRB3) gene is located on short arm of chromosome 8 and have two variants [c.491C.T(p.Trp64Arg) and c.1075C.G (pArg353Cys) 9]at a frequency of > 0.5%.Out of these, the variant at position 64 has attracted the most scientific interest.[4] . It was reported that although, there is no significant change in agonist binding properties for both variants, the impact on downstream signaling effects (adenylyl cyclase activation and cAMP formation) differed in the various cell lines[4].

In western obese patients, arginine form was associated with an increased susceptibility for weight gain and an increased tendency to develop .type 2 diabetes mellitus. [10]. The association was stronger for homozygous subjects in whom the relative risk for diabeters mellitus was 2.13 times higher than control. However, Some other studies [11-13] could not find any difference between diabetic and non diabetic individuals. These studies indicate that adrenergic receptor beta gene polymorphism and their association with disease susceptibility varies with race and ethnicity. Moreover, no study has been conducted to investigate if there is any impact of adrenergic receptor beta (ADRB2 and ADRB3) gene polymorphism on gut motility of type 2 diabetic individuals. Hence this present study was designed to find out the answer of above question in Indian settings.

Materials And Methods:

This study was carried out in the department of Gastroenterology and Endocrinology PGIMER, Chandigarh. It was conducted after receiving approval from the Institute ethics Committee, PGIME&R, Chandigarh, India. Detailed study design has been described in our previous studies [14-16] . In brief, 300 T2DM patients were recruited from Diabetes Clinic at PGIMER following American Diabetes Association 2013 criteria. Patients who developed diarrhoea following Metformin intake were not been included in this study. Moreover, patients with history of peptic ulcer and taking prokinetic therapies, broad spectrum antibiotics and proton pump inhibitors were excluded from this study. Age and sex matched 200 healthy subjects without diabetes and any gastrointestinal disorders were also included in this study as controls.

After enrolment, detailed clinical history including altered bowel habit such as constipation and/or diarrhoea , history of dietary intake and BMI were recorded.

For studying ADRB 2 and 3 gene polymorphism, DNA was isolated from buffy coat of EDTA blood sample using phenol chloroform method. Then the isolated DNA was subjected to Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP) using following primers: Beta 2-AR F: 5' CTTCTTGCTGGCACGCAAT-3', Beta- 2 AR R: 5' CCAGTGAAGTGATGAATAGTTGG 3' ; Beta 3-AR F 5' CGCCCAATACCGCCAACAC 3' Beta -3 AR R 5'-CCACCAGGAGTCCCATCACC- 3'

PCR amplification of both the genes was performed in Eppendorf master cycler using above mentioned specific primers.

PCR conditions for Beta-2 AR were: an initial denaturation step at 94^{o} C for 4 minutes , followed by 30 cycles of denaturation at 94^{o} C for 1 minute , annealing at 58 ^{o} C for 1 minute and extension at 72 ^{o} C for 1 minute, with a final extension of 10 minutes at 72 ^{o} C.

The amplified PCR product of 210 bp for Arg16 Gly was digested with BSeMI restriction enzyme. The fragments were resolved by electrophoresis on 6% acrylamide gels. Bands were visualized by UV trans illumination. 131 bp, 56 bp and 14 bp were observed in the gel for individual homozygote for Arg16Arg. 131 bp, 108 bp and 56 bp were observed in the gel for individual heterozygote for Arg16Gly and 108 bp &56 bp were observed for individual homozygote for Gly16Gly. (Figure 1a)

PCR conditions for Beta-3 AR were: an initial denaturation step at 94^{o} C for 5 minutes, followed by 33 cycles of denaturation at 94^{o} C for 30 seconds , annealing at 61 o C for 30 seconds , and extension at 72 o C for 15 seconds, with a final extension of 7 minutes at 72 ^{o} C.

The amplified PCR product of 210 bp was digested with BstNI restriction enzyme. The fragments were resolved on 6% acrylamide gel as before. The amplicon of 99,62,30,12,7 bp were observed in individual with genotype Trp64Trp (wild homozygous) , 161,99,62,30,12,7bp bands were observed in individuals with genotype Trp64Arg (variant homozygous) and 161,30,12,7 bp bands were observed in individuals with heterozygous Arg64Arg genotype . (bands of 14 bp, 12 bp, 7bp were too small to be visualized in the gel) (Figure 1b)

Hypo and hyper gut motility was assessed by measuring orocecal transit time (OCTT) according to the original method proposed by Jorge et al 1994[17] and modified subsequently by Rana et al 2010[18]. In brief, after ingestion of 10 g of lactulose, hydrogen concentration in fasting state and at every 15 minutes interval for 4 hours were measured in the end expiratory samples with the help of breath hydrogen Microlyzer from Quinton, USA.

Statistical analysis: Statistical analysis was carried out by SPSS 16.0 version. Data were presented as Mean± SEM and percentage. Independent T test was used to compare between cases and controls of

parameters with continuous numbers. Chi square test was carried out to compare categorical variables. P values less than 0.05 was considered significant.

Results:

Demographic characteristics were described earlier in details.[14, 15] In brief, out of 300 diabetic study participants, 142 were males and 96 were females. Mean age of diabetic individuals was 54.6 years (range 30-70 years). Males were older than females but not significantly different. Majority of study participants (59.6%) had constipation compared to only few patients (14.4%) having diarrhoea.

ADRB2 and ADRB3 gene polymorphism examined in the present study were following Hardy-Weinberg equilibrium ($p>0.05$). Distributions of ADRB2 and ADRB3 polymorphism, allele and genotype frequencies in patients and control have been presented in 1a and 1b. Representative gel picture for adrenergic beta receptor gene polymorphism on 6% acrylamide gel is shown in figure 1A and 1B. The frequency of A allele and AA genotype (ADRB2 A=G) was significantly higher in patients than controls and was associated with increased risk (A allele : OR, 1.46 , 95% CI 1.13-1.89); AA genotype: OR, 2.3; 95% CI, 1.34-3.74 p=0.0024). Similarly, frequency of C allele and CC genotype (ADRB3 C=T) was significantly higher in patients compared to controls. It was associated with increased risk (C allele: O R, 1.48, 95% CI 1.07-2.05 ; CC genotype : OR,5.72)

Gut motility and ADRB2 / ADRB3 polymorphism in T2DM patients and controls

In the present study the gut motility (OCTT) was significantly ($p<0.01$) prolonged in individuals with CC genotype (163.5±11.7minutes) compared to TT (125.2±4.0) or CT (144.6±6.1 minutes) genotype of ADRB3 polymorphism . On the other hand, no such significant difference was observed in OCTT in controls with CC genotype and CT genotype or TT genotype. However, controls with CT genotype (103.4±3.2 minutes) had significantly prolonged OCTT compared to TT genotype (94.2±2.7 minutes). (Figure 2a)

Similarly, in ADRB2 polymorphism, AA genotype had significantly prolonged (159.2±7.9 minutes) OCTT compared to GG (133.5 ±5.4 minutes) or AG (141.9±4.5 minutes). The trend of delayed OCTT was similar in controls: the OCTT was significantly prolonged in controls with AA (112.5±4.0 minutes) genotype as compared to GG (92.7±3.5 minutes) or AG (96.7±2.4 minutes) genotype. The polymorphism has role in both patients and controls but as the prevalence of AA genotype is more in T2DM patients as compared to controls producing more phenotypic effect compared to controls. (Figure 2b)

On analysis of combined effect of both ADRB3 and ADRB2 polymorphism on the gut motility (OCTT) , it was observed that when the individual has AA genotype , along with any combination be it TT+AG (148.2±4.7 minutes) / TT+AA (153.1±8.4 minutes) ; TC +AG (156.8±9.6 minutes) / TC +AA (163.5±9.8 minutes) and CC+AG (137.5 ±8.8 minutes) the OCTT was found to be prolonged except in CC+AA (120.7±3.5 minutes) . However, overall AA genotype has the dominant effect on gut motility.

Hyper and hypo gut motility in ADRB2/ADRB3 polymorphism

On the basis of gut motility measured by non-invasive lactulose hydrogen breath test T2DM patients were divided in to 2 groups: Hypomotility having OCTT more than 90 minutes and hypermotility having OCTT less than 90 minutes. It was observed that AA genotype (181.6± 5.8 minutes) had significantly prolonged gut motility compared to individuals with AG (166.8±4.2 minutes) or GG genotype (153.1±4.5 minutes). In case of hypomotility group of ADRB3 polymorphism, CC genotype (182.1±11.9 minutes) had significantly delayed gut motility compared to CT (164.7± 5.0 minutes) and TT (150.8±3.7 minutes) genotype. In case of hypermotility group, there was no significant difference between 3 genotypes of both ADRB2 and ADRB3 polymorphism (Figure 3a and 3b).

Gastrointestinal symptoms, Gut motility and ADRB2/B3 polymorphism:

Association between gastrointestinal symptoms, gut motility and ADRB2/ADRB3 polymorphism have been presented in Table 2. It was observed that significantly more number of diabetes patients with diarrhoea (28.7%) had GG genotype and OCTT was also significantly rapid in diabetic patients with diarrhoea who had GG (72.4 ±2.6 minutes) genotype as compared to patients with AG (82.7±3.5 minutes) genotype or AA (99.3±1.9 minutes) genotype. However, the data was not significant in terms of number of the individuals with constipation and OCTT though showed a delayed trend from patients having GG (147.2±3.3 minutes) < AG (154.2± 4.7 minutes) < AA (165.8 ±5.1 minutes) individuals but the data was not significant . The patients who had no problem mostly belong to AG genotype (32.7%) and the OCTT showed a non-significant decreasing trend with AA having the most delayed one.

In case of ADRB3, more number of diabetes patients with constipation belonged to CC genotype (80%) and CT genotype (78.7%). Moreover, OCTT was significantly prolonged in diabetic patients with constipation who had CC genotype and CT genotype than patients with TT genotype. On the contrary more number of diabetic patients presented with diarrhoea (19.2%) belonged to TT genotype and OCTT was fastest compared to CT and CC genotype but the data was not significant in terms of number of the individuals with diarrhoea and OCTT. Similar trend with non-significant fastest gut motility was also observed in TT genotype of diabetic patients who had no problem.

Discussion:

The beta 2adrenergic receptor, a member of the G protein coupled receptor, has more than 80 polymorphisms. Out of these, the Gly16 variants of the beta2 receptor displayed hyper functionality compared with Arg16 variant because of faster conformational changes following phosphorylation by GRKs[19].

The exome variant server currently listed 10 variants that have reproducibly been reported within the coding sequence of the ADRB3 gene. The most common B3 adrenoceptor variation, Trp64Arg has most intensely been investigated with regard to potential role in metabolic abnormalities.

In the present study frequency of A allele and AA genotype was significantly higher in patients than in controls and was associated with increased risk of T2DM. This shows that Arg16 variant was associated with increased disease susceptibility. This was in accordance with previous study conducted by Chang et al 2002 [7]who demonstrated in Taiwanese population that homozygous Arg16 variant of ADRB2 gene had higher frequency of association with the development of T2DM Moreover, this study contradicts the findings of other studies who suggested that the genetic variability in ADRB2 gene may not influence the development of obesity and diabetes in middle aged Korean populations [5, 9]..

The present study showed that the amino acid substitution (tryptophan to Arginine) at codon 64 of the beta 3 adrenergic receptor gene is present with an allelic frequency of 23% in type2 diabetic patients. The allelic frequency was higher than observed in Caucasian population (8-13%)[20, 21] and similar to those found in Pima Indians and Japanese subjects (30-37%) [22] [23]. The contribution of Trp64Arg polymorphism of the ADRB3 gene to the etiology of T2DM is still under debate. In the present study, frequency of C allele and CC genotype was significantly higher in patients than in controls and was associated with increased risk of T2DM. Many studies support these findings [5] [24]. However, some studies reported contradictory results having no association between ADRB3 gene polymorphism and susceptibility to T2DM[10, 11, 25] . This discrepancy in findings on the association of ADRB2/ ADRB3 gene polymorphism with T2DM may be due to racial and ethnic differences in the risk for diabetes

In the present study, it was observed that OCTT was significantly prolonged in individuals with AA genotype as compared to GG or AG genotype. The trend of delayed OCTT was similar in controls also. Similarly, with respect to ADRB3 gene polymorphism, the OCTT was significantly prolonged in individuals with CC genotype as compared to TT or CT genotype. The polymorphism has role in both patients and controls but as the prevalence of AA /CC genotype is more in type 2 diabetic patients compared to controls, the phenotypic effect is more in them. Moreover, it was observed that in patients with AA genotype the gut hypo-motility was significantly delayed compared to individuals with AG or GG genotype. In case of ADRB3 gene polymorphism, it was observed that in patients with CC genotype, the gut hypo motility was significantly delayed compared to individuals with CT or TT genotypes. Studies comparing the ADRB2/ADRB3 polymorphism with the gut motility are not documented in literature. However, few studies showing the role of adrenergic receptor beta2 /3 in the gut motility are available. According to Ahluwalia et al 1994,[26] the beta 2 adrenergic receptors seem to influence the speed of nutrient transit in the human small bowel. In healthy volunteers both orocecal and duodenal transit times were accelerated by propranolol which is a beta 2 agonist. Beta 3 receptor agonists have been shown to inhibit motility both in vivo as well as exvivo studies.[2, 27-29] . Also beta 3 adrenergic receptor agonists slowed transit time in wild type but not in the knock out mice.[30] . However, later on Grudell et al 2008 [31]reported that beta 3 adrenergic receptor agonist did not drastically affect colonic transit in patients even after 7 days of administration .

The present study revealed that significantly more number of diabetes patients with diarrhoea had GG genotype and OCTT was also significantly rapid in those patients. However, the data was not significant in patients with constipation as well as patients who had no GI symptoms. Similarly more number of

patients with constipation (80%) had CC genotype. Interestingly, OCTT was significantly prolonged in these diabetic patients who had CC genotype. On the contrary more number of patients with diarrhoea (19.2%) had TT genotype and OCTT was faster in these patients compared to other genotypes although the difference was not statistically significant. Present study is the first study to investigate the association of adrenoceptor (ADRB2/3) polymorphism with gut motility and the most common gastrointestinal symptoms like constipation and diarrhoea in T2DM.. In one study, [32] the authors have compared the polymorphism with bowel symptom severity and health related quality of life in irritable bowel syndrome (IBS) patients. They observed that in IBS, G allele carriers had a higher gastrointestinal symptom severity and frequency when compared with CC homozygotes.

Considering the combined effect of ADRB2 and ADRB3 gene polymorphisms on gut motility, it is evident that AA genotype of ADRB2 has dominant effect on the gut motility. Even in the presence of A allele i.e. in AG genotype there is delay in gut motility. However, as per the individual effects of CC and AA, the combined effect should have more delay in the gut motility but this could not be observed in this study which may be due to very few (3) number of patients enrolled in this combination. Since there is no study available in literature we could not compare our findings with other findings.

Conclusion:

In short, this study documented that AA genotype in case of ADRB2 polymorphism and

CC genotype in case of ADRB3 polymorphism was significantly higher in T2DM patients compared to healthy controls. Moreover, AA and CC genotype of ADRB2 and ADRB3 gene polymorphism respectively had significantly prolonged gut motility compared to other genotypes and presented with constipation. Moreover, combined effect of these two polymorphisms (ADRB2 and ADRB3) revealed that the presence of “A” allele has the dominant effect on gut motility in T2 DM patients. Therefore, it could be concluded that AA genotypes are prone to develop gastrointestinal symptoms because of delayed gut motility. Hence, this polymorphism study would help T2DM patients to identify the vulnerable genotypes and help in developing preventive measures in the form of modulation of lifestyle in order to prevent appearance of symptoms associated with altered gastrointestinal motility and improves quality of life in T2DM patients.

Declarations

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Data availability : All data generated or analyzed during this study are included in this article

Compliance with ethical standards Conflict of interest : The authors declare that they have no competing interests.

Ethical approval: Ethical approval was received from from the Institute ethics Committee, PGIME&R, Chandigarh, India.

Consent to participate: Written informed consent was obtained from all individuals according to the guidelines of the Institutional Review Board for human studies at PGIME&R, Chandigarh, India.

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Tables

Table1a: Allele frequencies of the ADRB2 and ADRB3 polymorphism in T2DM patients and controls

	T2DM (2n=600)	Controls (2n=400)	OR (95% CI)	P value
ADRB2	G=285 (0.475)	G= 228 (0.57)	---	---
	A=315 (0.525)	A=172 (0.43)	1.46 (1.13-1.89)	<0.01
ADRB3	T=462 (0.77)	T=333 (0.832)	----	----
	C=138 (0.23)	C= 67 (0.167)	1.48 (1.07-2.05)	<0.05

ADRB2: Adrenergic receptor beta 2; ADRB3: Adrenergic receptor beta 3

Table 1b: Genotype frequencies of ADRB2 and ADRB3 polymorphism in T2DM patients and controls

	T2DM (n=300)	Controls (n= 200)	OR (95%CI)	P value
ADRB2	GG=66 (22%)	GG=60 (30%)	Ref	---
	AG =153 (51%)	AG = 108 (54%)	1.29 (0.84-1.93)	NS
	AA 81 (27%)	AA=32 (16%)	2.3 (1.34-3.74)	0.0024
ADRB3	TT=177 (59%)	TT=135 (67.5%)	Ref	---
	CT=108 (36%)	CT= 63 (31.5%)	1.31 (0.89-1.92)	NS
	CC=15 (5%)	CC =2 (1%)	5.72	<0.05

ADRB2: Adrenergic receptor beta 2; ADRB3: Adrenergic receptor beta 3

Table 2: Gastrointestinal symptoms, Gut motility and ADRB2/ADRB3 polymorphism in T2DM patients and controls

ADRB2	**GG**	**AG**	**AA**	**Significance**
	N=66	**N=153**	**N=81**	
Constipation	39(59.1%)	86(56.2%)	54(66.7%)	NS
N=179	147.2±3.3	154.2±4.7	165.8±5.1	
Diarrhoea	19(28.7%)	17(11.1%)	7(8.6%)	AA vs GG<0.01
N=43	72.4±2.6	82.7±3.5	99.3±1.9	χ^2 =8.8 df=1 AA vs AG NS AG vs GG<0.01 χ^2 =9.2 df=1 OCTT AA vs GG<0.0001 AG vs GG <0.05
No problem	8 (12.2%)	50 (32.7%)	20 (24.7%)	AA vs GG NS
N= 78	94.8±2.0	100.7±4.9	104.5±3.8	AA vs AG NS AG vs GG <0.01 χ^2 =8.9 df=1 OCTT NS
ADRB3	**TT**	**CT**	**CC**	
	N=177	**N=108**	**N=15**	
Constipation	82 (46.3%)	85(78.7%)	12 (80%)	CCvs TT <0.05
N=179	139.7±5.5	158.6±7.4	186.4±9.1	χ^2 =4.9 df=1 CT vs CC NS CT vsTT <0.001 χ^2 =27.6 df=1 OCTT CC vs TT&CT vs TT<0.05

Diarrhoea	34(19.2%)	8(7.4%)	1(6.7%)	TT vs. CC :NS
N=43	80.9±6.2	100.4±3.2	105	
No problem	61 (34.5%)	15(13.9%)	2(13.3%)	TT vs. CC: NS
N=78	95.9±4.3	108.3±5.7	112.5±7.4	OCTT: NS

OCTT: Orocecal transit time, NS: not significant, ADRB2: Adrenergic receptor beta 2; ADRB3: Adrenergic receptor beta 3

Figures

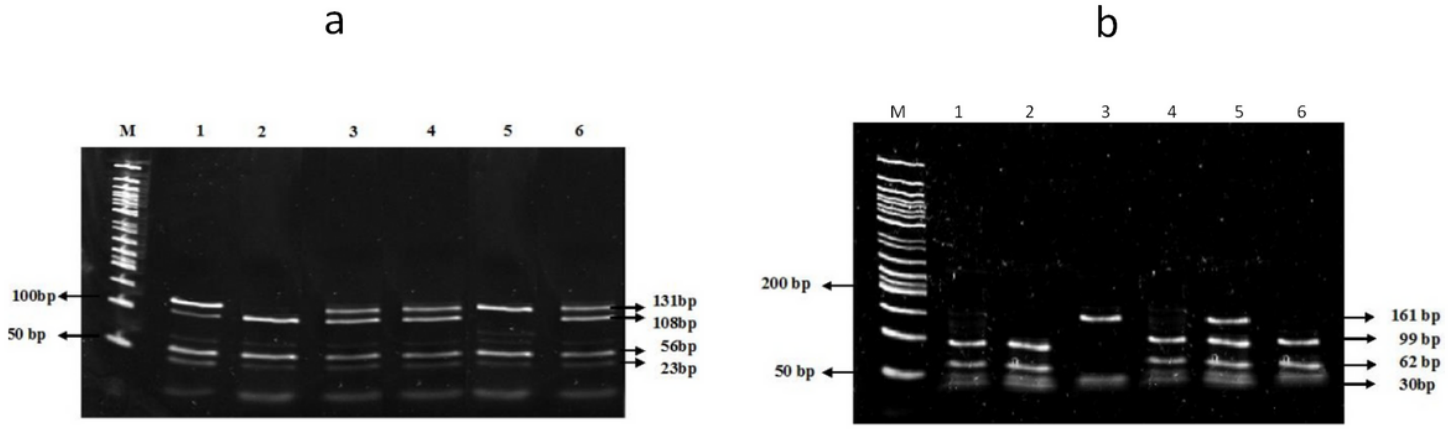

Figure 1

a: Adrenergic receptor beta 2 polymorphism by polymerase chain reaction represented on 6% acrylamide gel • Lane 1 Arg 16 Gly (AG) • Lane 2 Gly16Gly (GG) • Lane 3 Arg16 Gly (AG) • Lane 4 Arg16 Gly (AG) • Lane 5 Arg16Arg (AA) • Lane 6 Arg16 Gly (AG) b: Adrenergic receptor beta 3 polymorphism by polymerase chain reaction represented on 6% acrylamide gel • Lane 1Trp64Trp (TT) • Lane2 Trp64Trp (TT) • Lane 3 Arg64Arg (CC) • Lane 4 Trp64Trp (TT) • Lane 5 Trp64Arg (CT) • Lane 6 Trp64Trp (TT)

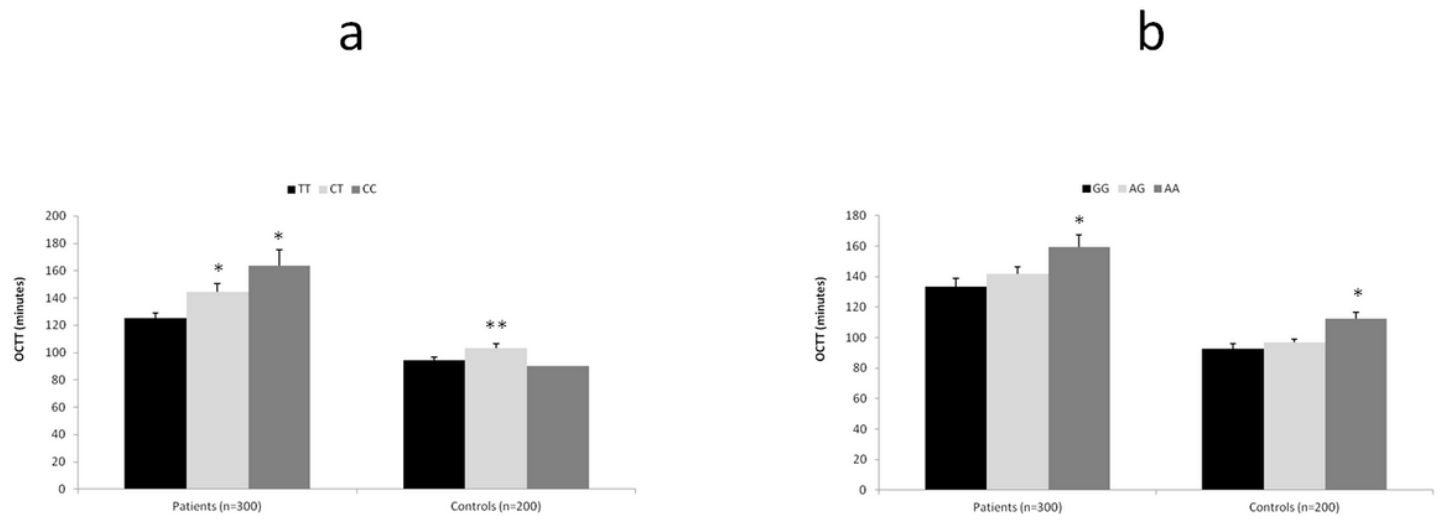

Figure 2

a: Gut motility (OCTT in minutes) and ADRB3 polymorphism in T2DM patients and controls • Results are expressed as Mean ± SEM • *p<0.01: TT vs. CC and CT in T2 DM patients & **p< 0.05 TT vs. CT in healthy controls • OCTT: Orocecal transit time, ADRB3: Adrenergic receptor beta 3 b: Gut motility (OCTT in minutes) and ADRB2 polymorphism in T2DM patients and controls • Results are expressed as Mean ± SEM • *p< 0.05 AA vs GG, AG in T2DM patients & AA vs GG, AG in healthy controls • OCTT: Orocecal transit time , ADRB2: Adrenergic receptor beta 2

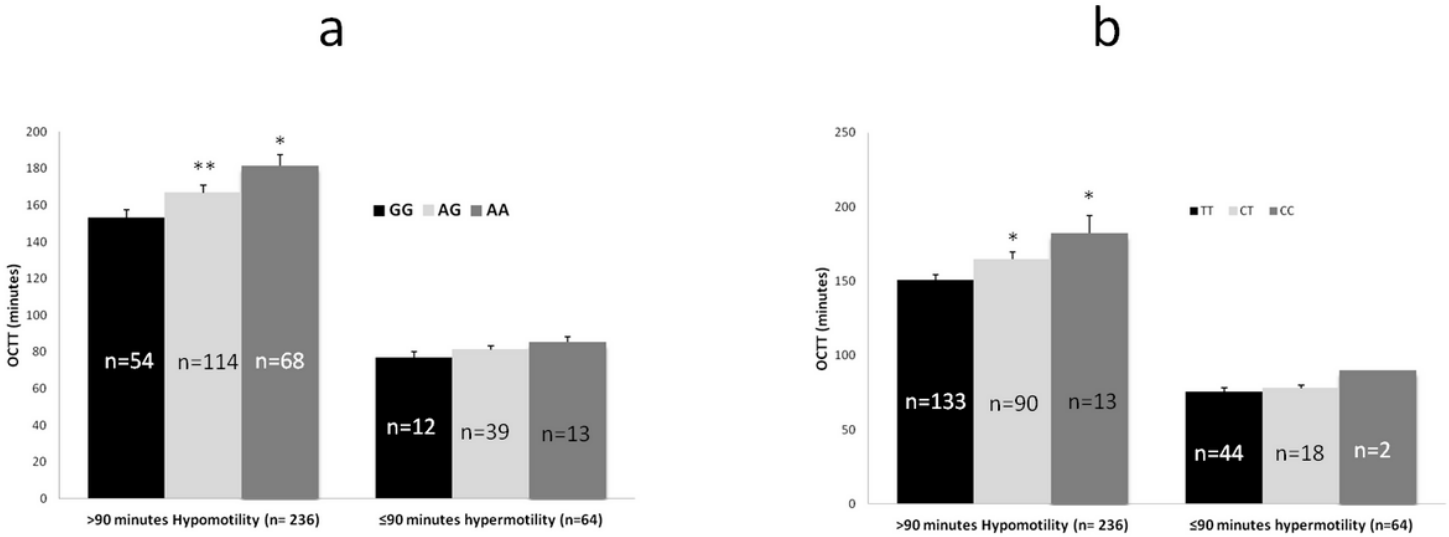

Figure 3

a: Hyper and hypo gut motility (minutes) in ADRB2 polymorphism in type 2 diabetes mellitus patients and controls • Results are expressed as Mean ± SEM • *P<0.01 AA vs. GG, AG for hypo motility in T2DM patients • **P<0.05 AG vs. GG for hypo motility in type 2 diabetes mellitus • OCTT: Orocecal transit time, ADRB2: Adrenergic receptor beta 2 b: Hyper and hypo gut motility (minutes) in ADRB3 polymorphism in

type 2 diabetes mellitus patients and controls • Results are expressed as Mean ± SEM • *P<0.05 CC vs. TT & CT vs. TT for hypo motility in type 2 diabetes mellitus • OCTT: Orocecal transit time, ADRB3: Adrenergic receptor beta 3