Research Article **CODEN: IJRPJK** **ISSN: 2319 – 9563**

International Journal of Research in Pharmaceutical and Nano Sciences

Journal homepage: **www.ijrpns.com**

STUDY OF MECHANISM OF INSULIN RESISTANCE IN TYPE-II DIABETES PATIENTS

S. Sdharsheni*[1]

[1*]Department of Pharmacy Practice, Trichy, Tamil Nadu, India.

ABSTRACT

Type 2 diabetes mellitus is a serious and widespread metabolic disorder associated with dysregulation of carbohydrate and lipid metabolism. In chronic conditions, it leads to numerous complications resulting into diabetic neuropathy, nephropathy and retinopathy and in extreme disease conditions; it is also associated with cardiovascular disorders. There is need for the early diagnosis and treatment of this syndrome, so that its later stage complications can be avoided or minimized. The aim of this study is to obtain further insight in the mechanisms contributing to the development of insulin resistance and type 2 diabetes in humans. Our hypothesis is that insulin resistance is not caused by a primary target cell defect and that neural or humoral factors may contribute to the development of insulin resistance. In this study, there are signs of dysregulation in the autonomic nervous system, the cortisol axis, adipose tissue distribution and adipokine production in insulin resistance associated with type 2 diabetes. An altered balance in any of these insulin-antagonistic systems due to genetic and/or environmental factors may be a contributing factor in the development of insulin resistance seen in the metabolic syndrome and type 2 diabetes.

KEYWORDS

Insulin Resistance, Type-II Diabetes Patients and Oral glucose tolerance.

Author for Correspondence

Sdharsheni S,
Department of Pharmacy Practice,
Trichy, Tamil Nadu, India.

Email: sdharshini3@gmail.com

INTRODUCTION

Diabetes was one of the first diseases described, with an Egyptian manuscript from c. 1500 BCE mentioning "too great emptying of the urine". The first described cases are believed to be of type 1 diabetes. Indian physicians around the same time identified the disease and classified it as *madhumeha* or "honey urine", noting the urine would attract ants[1]. The term "diabetes" or "to pass through" was

first used in 230 BCE by the Greek Appollonius of Memphis. The disease was considered rare during the time of the Roman empire, with Galen commenting he had only seen two cases during his career[2].

There are three main types of diabetes mellitus: Type 1 DM results from the body's failure to produce enough insulin. This form was previously referred to as "insulin-dependent diabetes mellitus" (IDDM) or "juvenile diabetes". The cause is unknown. Type 2 DM begins with insulin resistance, a condition in which cells fail to respond to insulin properly. As the disease progresses a lack of insulin may also develop. This form was previously referred to as "non-insulin-dependent diabetes mellitus" (NIDDM) or "adult-onset diabetes". The primary cause is excessive body weight and not enough exercise. Gestational diabetes, is the third main form and occurs when pregnant women without a previous history of diabetes develop a high blood glucose level[3]. Insulin's name is derived from the Latin *insula* for "island". Insulin's structure varies slightly between species of animals. Insulin from animal sources differs somewhat in "strength" (in carbohydrate metabolism control effects) from that in humans because of those variations. Insulin is produced in the pancreas and released when any of several stimuli are detected. These stimuli include ingested protein and glucose in the blood produced from digested food. Special transporter proteins in cell membranes allow glucose from the blood to enter a cell. These transporters are, indirectly, under blood insulin's control in certain body cell types (e.g., muscle cells). Low levels of circulating insulin, or its absence, will prevent glucose from entering those cells (e.g., in type 1 diabetes). Activation of insulin receptors leads to internal cellular mechanisms that directly affect glucose uptake by regulating the number and operation of protein molecules in the cell membrane that transport glucose into the cell. The genes that specify the proteins that make up the insulin receptor in cell membranes have been identified, and the structures of the interior, transmembrane section, and the extra-membrane section of receptor have been solved[4]. Insulin resistance (IR) is a physiological condition in which cells fail to respond to the normal actions of the hormone insulin. The body produces insulin, but the cells in the body become resistant to insulin and are unable to use it as effectively, leading to hyperglycemia. Beta cells in the pancreas subsequently increase their production of insulin, further contributing to hyperinsulinemia. This often remains undetected and can contribute to a diagnosis of Type 2 Diabetes or latent autoimmune diabetes of adults[5-9].

The aim of this study is to obtain further insight in the mechanisms contributing to the development of insulin resistance and type 2 diabetes in humans. Our hypothesis is that insulin resistance is not caused by a primary target cell defect and that neural or humoral factors may contribute to the development of insulin resistance.

MATERIAL AND METHODS

Study sample The study population consisted of all patients receiving their primary care from Private hospital in Hyderabad (2010) was selected. Study sample was selected after application of a set of inclusion and exclusion criteria to overcome inconsistencies in data recording procedures.

Inclusion criteria

All patients aged more than 18 years to less than 90 years were included in the study. All outpatients receiving their medication.

Exclusion criteria

Patients with no single visit to a clinic which provides chronic diabetic care were excluded from the study. Patients who did not have their first diabetes medication prescription from a clinic providing primary care for diabetes listed in appendix A were excluded because we could not ascertain the if the patients were newly treated or patients receiving a continuation in diabetes care.

Case I-III

30 non-diabetic subjects in the ages 20 to 43 years, were selected in private hospital. The groups were well matched according to BMI, gender and age. 16 were males and 14 females. 2 diabetes relatives had impaired glucose tolerance. They were otherwise all

in good health as determined by medical history, clinical examination and laboratory tests including hematology, serum electrolytes, creatinine and serum lipids. None of the subjects received any chronic medication[10, 11].

Case-IV

In study IV, 30 subjects were selected from Diabetes Unit of private hospital in Hyderabad. 20 were type 2 diabetic patients, ten with poor and ten with good metabolic control, defined according to HbA1c levels. All subjects were otherwise in good health as determined by medical history, clinical examination, ECG and blood tests including hematology, serum electrolytes, creatinine, serum lipids and liver enzymes. Of the diabetic subjects, 7 had no pharmacological treatment; seven were treated with sulfonylurea alone, four with sulfonylurea and metformin in combination. One subject was treated with repaglinide alone and one subject with repaglinide and metformin in combination[12,13].

Oral glucose tolerance test (OGTT)

The subjects in case I-III underwent an OGTT. Venous blood samples for determination of blood glucose and serum insulin were obtained before and 120 minutes after ingestion of 75 g glucose in a liquid solution. 2-h blood glucose values of 6.7-9.9 were defined as impaired glucose tolerance[14, 15].

Statistical analyses

Statistical analyses were performed using the SPSS package. Data are means±SEM unless otherwise is indicated.

RESULTS AND DISCUSSION

Study of insulin resistance

Study population consisted of all patients receiving their primary care from Private hospital in Hyderabad (2010) was selected. The patient history is given in Table No.1 and medication patterns are given in Table No.2 and Figure No.1. The interplay between insulin resistance, steroid hormones and leptin was explored in 33 healthy relatives of type 2 diabetes patients and 33 age-, sex- and BMI-matched control subjects without a family history of diabetes. The diabetes relatives were more insulin resistant than control subjects, when gender was analysed separately, this was significant only in males. Male relatives displayed lower morning cortisol and testosterone levels and higher leptin levels compared to male control subjects. Leptin levels were negatively associated with insulin sensitivity in male and female relatives and in male controls ($r= -0.66$, $r= - 0.67$ an $r= -0.49$, respectively, $p<0.05$). In the female control group this association was nearly significant ($r= -0.51$, $p=0.063$). There were no significant associations between insulin resistance and cortisol levels. The possible interplay between insulin resistance and the activity in the autonomic nervous system was investigated in 15 healthy type 2 diabetes relatives and 15 sex-, age- and BMI-matched control subject without a family history of diabetes. When dividing the total cohort into two groups based on their M-value, the group with low M-value exhibited signs of a higher sympathetic/parasympathetic ratio ($p=0.04$) and lower parasympathetic activity during controlled breathing and cold pressure test ($p=0.01$ and $p=0.03$, respectively) compared with the group with high M-value. In general, the insulin-resistant group displayed lower reactivity in the autonomic nervous system upon provocations. Adipose tissue distribution and the regulation of the cortisol axis were examined and the association with insulin resistance and the activity in the autonomic nervous system were evaluated in 15 healthy relatives of type 2 diabetes patients and 15 age-, sex- and BMI-matched control subjects without a family history of diabetes. There were no significant associations between SAT and insulin resistance, the cortisol axis activity or the activity in the autonomic nervous system (Table No.3, 4 and Figure No.2, 3).

Table No.1: Patient history

S.No	Patients	R value	P value
1	Diabetic patient	0.48 (male)	0.04
2	Relatives patient	-0.66, -0.67 (male, female)	0.05

Table No.2: Medication utilization patterns

S.No	Medication class	Number of patients (N = 54)	
		N	%
1	Sulphonylurea	45	76
2	Thiazolidinedione	7	11
3	Insulin	7	11
4	Other (Sitagliptin)	1	2

Table No.3: Clinical and metabolic features of case-I-III (Control)

S.No	Subject	Age	Sex	Relative weight	Fasting serum glucose	2-h serum Glucose (GTT)	Fasting serum Insulin concentration	Mean adipocyte Size (pl/cell)
Control								
1	1	44	F	0.86	88	124	7	170
2	2	23	F	0.86	78	133	6	161
3	3	29	F	1.13	75	102	13	348
4	4	29	M	0.85	89	131	10	184
5	5	32	F	1.05	82	85	10	169
6	6	37	F	0.92	90	119	6	225
7	7	28	M	1.13	91	124	11	206
Mean		**35±3**		**0.97±0.05**	**85±2**	**117±7**	**9±1**	**209±25**

Table No.4: Clinical and metabolic features of case-I-III (Diabetic)

S.No	Subject	Age	Sex	Relative weight	Fasting serum glucose	2-h serum Glucose (GTT)	Fasting serum Insulin concentration	Mean adipocyte Size (pl/cell)
Control								
1	1	28	F	1.89	81	150	64	463
2	2	31	F	2.19	70	121	35	828
3	3	45	F	1.85	121	187	83	783
4	4	49	M	1.71	69	128	23	362
5	5	58	F	1.26	90	134	32	767
6	6	24	F	1.76	88	151	86	393
7	7	50	F	1.71	99	210	38	405
Mean		**40±4**		**1.71±0.09**	**90±6**	**162±11**	**54±8**	**570±64**

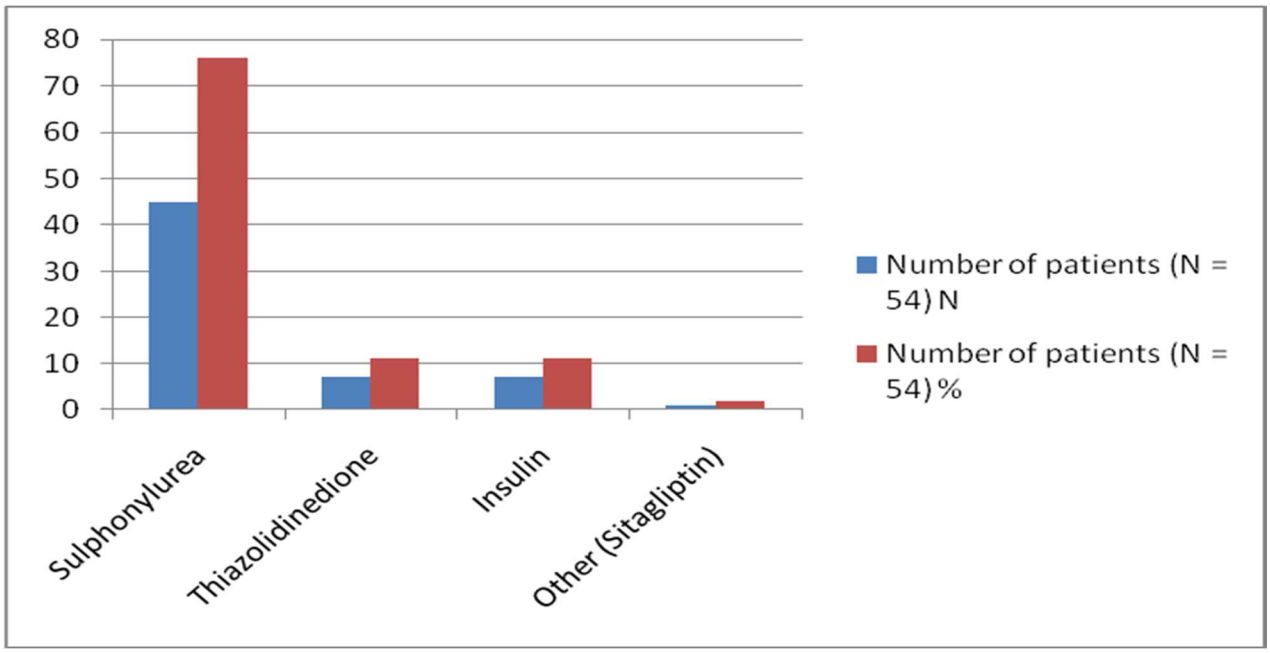

Figure No.1: Medication utilization patterns

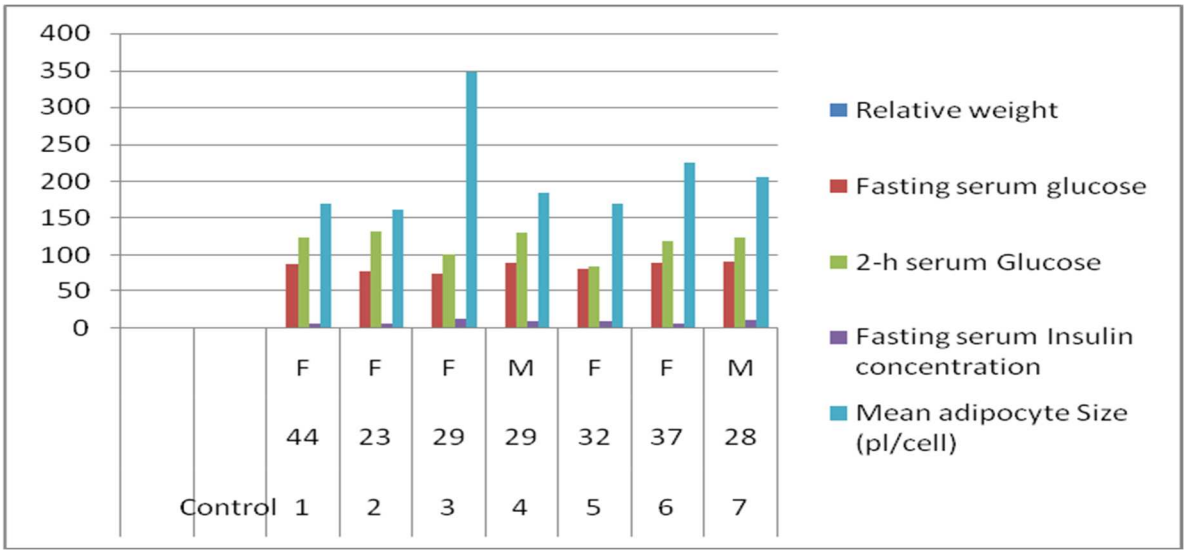

Figure No.2: Shows clinical and metabolic features of case-I-III (Control)

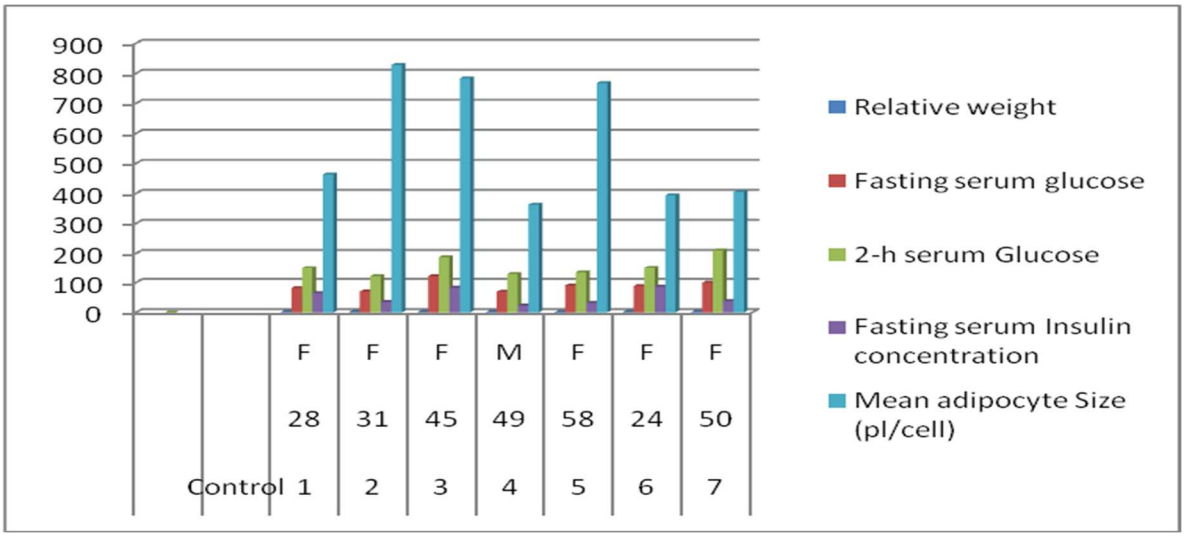

Figure No.3: Shows clinical and metabolic features of case-I-III (Diabetic)

CONCLUSION

Male subjects predisposed for type 2 diabetes display abnormalities in leptin, cortisol and testosterone levels. Insulin resistance was associated with high leptin levels and, in males, with low testosterone levels. An altered balance and reactivity in the autonomic nervous system appeared to be associated with insulin resistance.

ACKNOWLEDGEMENT

Author is thankful to the Private hospital in Hyderabad for carry out the research work.

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

REFERENCES

1. Ripoll. Diabetes Blue Circle Symbol", *International Diabetes Federation*, 2006.
2. Leonid Poretsky. Principles of diabetes mellitus, *New York: Springer*, 2nd edition, 2009, 3.
3. Shi Y and Frank B. The global implications of diabetes and cancer, *The Lancet*, 383(9933), 1993, 1947-1948.
4. Kitabchi A E, Umpierrez G E, Miles J M and Fisher J N. *Diabetes Care*, 32(7), 2009, 1335-1343.
5. Riserus U, Willett W C and Hu F B. Dietary fats and prevention of type 2 diabetes, *Prog Lipid Res*, 48(1), 2008, 44-51.
6. Malik V S, Popkin B M, Bray G A, Despres J P and Hu F B. Sugar Sweetened Beverages, Obesity, Type 2 Diabetes and Cardiovascular Disease risk, *Circulation*, 121(11), 2010, 1356-1364.
7. Fasanmade O A, Odeniyi I A and Ogbera A O. Diabetic ketoacidosis: diagnosis and management, *African J Med Medical Sci*, 37(2), 2008, 99-105.
8. Ripsin C M, Kang H and Urban R J. Management of blood glucose in type 2 diabetes mellitus, *Am Fam Physician*, 79(1), 2009, 29-36.
9. David G and Gardner. Greenspan's basic and clinical endocrinology, *New York: McGraw-Hill Medical*, 9th edition, 2008.
10. Kim E and Barrett. Ganong's review of medical physiology, *New York: McGraw-Hill Medical*, 20th edition, 2008.
11. Robert K and Murray. Harper's illustrated biochemistry, *New York: McGraw-Hill Medical*, 27th edition, 2009.
12. Willi C, Bodenmann P, Ghali W A, Faris P D and Cornuz J. Active smoking and the risk of type 2 diabetes: a systematic review and meta-analysis, *JAMA: the Journal of the American Medical Association*, 298(22), 2007, 2654-2664.
13. Nathan D M, Cleary P A, Backlund J Y, Genuth S M, Lachin J M, Orchard T J, Raskin P and Zinman B. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes, *The New England Journal of Medicine*, 353(25), 2005, 2643-2653.
14. Alzira M, Ferreira S and Jorge A. Insulin or insulin-like studies on unicellular organisms: a review, *Braz ArchBiol Technol*, 56(1), 2005, 47-49.
15. Le Roith D, Shiloach J, Heffron R, Rubinovitz C, Tanenbaum R and Roth J. Insulin-related material in microbes: similarities and differences from mammalian insulins, *Can J Biochem Cell Biol*, 63(8), 1985, 839-849.

Please cite this article in press as: Sdharsheni S. Study of mechanism of insulin resistance in type-ii diabetes patients, *International Journal of Research in Pharmaceutical and Nano Sciences*, 3(4), 2014, 337-343.