Journal of Mathematics and System Science 5 (2015) 252-261
doi: 10.17265/2159-5291/2015.06.004

Study of the Effects of FFA and Obesity on Diabetes Through Numerical Simulation of the Mathematical Model

Saloni Rathee, Nilam

Department of Applied Mathematics, Delhi Technological University, Main Bawana Road, Shahbad Daulatpur, Delhi-110042, India.

Received: February 27, 2015 / Accepted: March 23, 2015 / Published: June 25, 2015.

Abstract: Aim of the study is to analyze the effect of FFA together with the obesity on the glucose - insulin dynamics of NIDD people through a mathematical model. An attempt has been made to capture the glucose and insulin concentration levels for NIDD people having raised level of FFA and obesity through numerical simulation of the model. It has been observed from the simulation of the model that elevated level of plasma FFA inhibit glucose uptake, glucose utilization, decrease insulin sensitivity and increase insulin resistance in NIDD people in comparison to the normal people.

Keywords: Diabetes, NIDD, obesity, FFA, modeling, simulation.

1. Introduction

Type 2 diabetes mellitus also known as non insulin dependent diabetes (NIDD) is mainly characterized by raised sugar level in the context of lack of insulin or increased insulin resistance in the body. NIDD makes up approximately 90% of the cases of diabetes, while rest of 10% is primarily due to type 1 diabetes and gestational diabetes. Insulin resistance is the major reason behind the occurrence of type 2 diabetes. Insulin resistance can have many causes [1], but so far obesity is considered to be one of the major causes in the developed countries. The exact reason of how obesity cause insulin resistance is not fully known so far. But in US, obesity is approaching epidemic proportion where more than 2/3 of all adults are either overweight or obese [2].

Obesity is associated with elevated plasma free fatty acids (FFA) levels, with insulin resistance and hyperinsulinemia, two important cardiovascular risk factors for diabetes [3]. Obesity has a great impact on the glucose effectiveness and insulin sensitivity of any human body system. Infact Hofman [4] found that insulin sensitivity was approximated 80% lower in obese horses than in non-obese horses, an effect similar to reported 76 % reduction in insulin sensitivity in obese vs. non - weight humans [5]. Lowering of plasma FFA levels would improve insulin resistance, hyperinsulinemia and glucose tolerance in obese non diabetic and diabetic subjects.

Free Fatty Acids (FFA) are one of the outcomes of the food digestion process and these acids are described as “free” because they are freely transported in the bloodstream without the help of any other carrier and source [6]. Fatty acids are called essential fatty acids as they are required by the human body but cannot be provided in sufficient quantity by other substrates, hence must be obtained from food [6]. The relationship between obesity, FFA and type 2 diabetes is explained in Fig. 1.

Elevation of plasma FFA levels produce peripheral insulin resistance and increase hepatic insulin resistance in healthy obese and type 2 diabetic

Corresponding author: Nilam, Department of Applied Mathematics, Delhi Technological University, India.
E-mail: rathi.nilam@gmail.com.

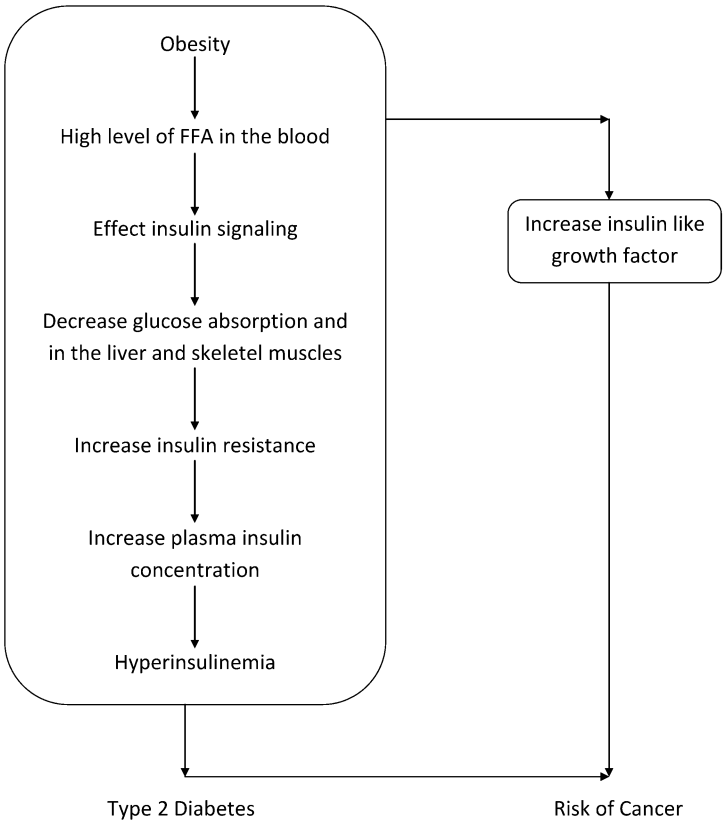

Fig 1 Relationship of obesity, FFA and type 2 diabetes.

Subjects. Plasma levels are elevated in most obese people and also physiological elevations of plasma FFA inhibit insulin mediated glucose uptake in a dose dependent fashion [6]. FFA not only increase insulin resistance [7,8,9] but also affect insulin secretion in normal as well as in diabetic people [10]. Glycogen synthesis in euglycemic diabetes patients were decreased to an even greater degree than rate of glucose uptake (-72 vs - 53%) [9]. The changes in plasma FFA and lactate noted over 24 hr study period in the patients with severe NIDD are consistent with the view that elevated plasma FFA and lactate levels plays an important role in the development of fasting hyperglycemia in patients with NIDDM [11]. Fatty acids caused a dose - dependent inhibition of insulin mediated glucose uptake. FFA and glycerol increase insulin suppressed hepatic glucose production and thus caused insulin resistance in the whole body. Glucose uptake decreased by ~50% (from 8.8 to 4.2 mg/kg/min) when FFA concentration rose from ~50 to ~750 μM. When FFA concentration rose from ~50 to ~500 μM, glucose uptake decreases by ~3 mg/kg/min, CHO oxidation and glucogen synthesis also decreases. Decline in glucose uptake, which occurred when plasma FFA concentration rose further (~550 to ~750 μM), was caused exclusively by a decrement in glycogen synthesis [8]. Also Boden [9] found the effect of fat on insulin mediated glucose uptake, as there was about 86% inhibition of the glucose uptake in isoglycemic patients with NIDD for insulin stimulated part and fat decrease glucose uptake by 46% during euglycemic clamping. It was found that adolescent obesity, obesity and persistent obesity from adolescence to young adulthood conferred the greatest likelihood of diabetes in young adulthood [12].

Mathematical modeling of the glucose - insulin dynamics of the diabetic patient affected by the

elevated FFA plasma level and obesity will helps to find the ways to maintain the glucose concentration under physiological range. To the time, theoretical evidences are given by many researchers about the strong link between raised FFA level, obesity and diabetes but still it is unfold mathematically.

Since it is evident from the past research articles that FFA and obesity are closely associated with diabetes, therefore an attempt has been made to analyze the effect of elevated FFA level and obesity on the glucose - insulin dynamics of diabetic people. This study will help to understand the effects of FFA and obesity on diabetes in a more efficient and mathematical way. Theoretical changes suggested by Boden has been incorporated in the mathematical model and then simulation has been carried out by using Matlab 2012b. The simulated concentrations of glucose, plasma insulin and remote insulin levels of normal and NIDD people are compared and given in Table 3, Table 4 and Table 5. There is a strong relation between obesity and FFA [11], which are amongst the main factors responsible for occurrence of type 2 diabetes. FFA also cause hepatic insulin resistance by inhibiting insulin suppression of glycogenolysis [13]. On the basis of theoretical results obtained by Boden [9], the effect of physiological elevation of plasma FFA on the glucose and insulin concentration level for obese people having type 2 diabetes through a mathematical model will be discussed in the present study.

The minimal model [14] for the glucose - insulin dynamics is given as

$$\frac{dG(t)}{dt} = -X(t)G(t) - p_1(G(t) - G_b), G(0) = G_0 \quad (1)$$

$$\frac{dX(t)}{dt} = -p_2X(t) + p_3(I(t) - I_b), X(0) = X_0 \quad (2)$$

$$\frac{dI(t)}{dt} = -p_4(I(t) - I_b) + p_5(G(t) - G_c)^+t, I(0) = I_0 + I_b \quad (3)$$

Where, $G(t)$ [mg/dl] represents glucose concentration at time t, $X(t)$ [min^{-1}] represents remote insulin concentration at time t, $I(t)$ [$\mu U/ml$] represents the plasma insulin at time t, G_b [mg/dl] represents the basal glucose level, G_c [mg/dl] represents the threshold glucose level of glucose above which the endogenous insulin secretion will be stimulated and I_b [$\mu U/ml$] represents the basal insulin level. The parameters p_i ($p_i > 0$), i = 1,2,3,4,5 are given in Table 1.

Table 1 The parameters related to the model.

Parameters	Units	Explanation	References
p_1	min^{-1}	represents glucose effectiveness	[14]
p_2	min^{-1}	fractional rate of insulin clearance from the remote compartment	[14]
p_3	(min^{-2}) (μ U/ml) $^{-1}$	contribution of plasma insulin to the remote compartment	[14]
p_4	min^{-1}	clearance of plasma insulin	[14]
p_5	(min^{-2}) (μ U/ml) $(mg/dl)^{-1}$	degree by which glucose exceeds threshold or baseline glucose level	[14]

Table 2 The values of the parameters.

Parameters	value for normal	references	value for NIDD	references
p_1	0.399e-01	[16]	0.14e-01	[15]
p_2	0.200e-01	[16]	0.200e-01	[15]
p_3	0.4e-04	[16]	0.24e-05	-
p_4	0.257	[16]	0.129	[15]
p_5	0.001	[16]	0.0015	-
G_0	287.	[16]	392.	[15]
I_0	351.	[16]	1322.	[15]

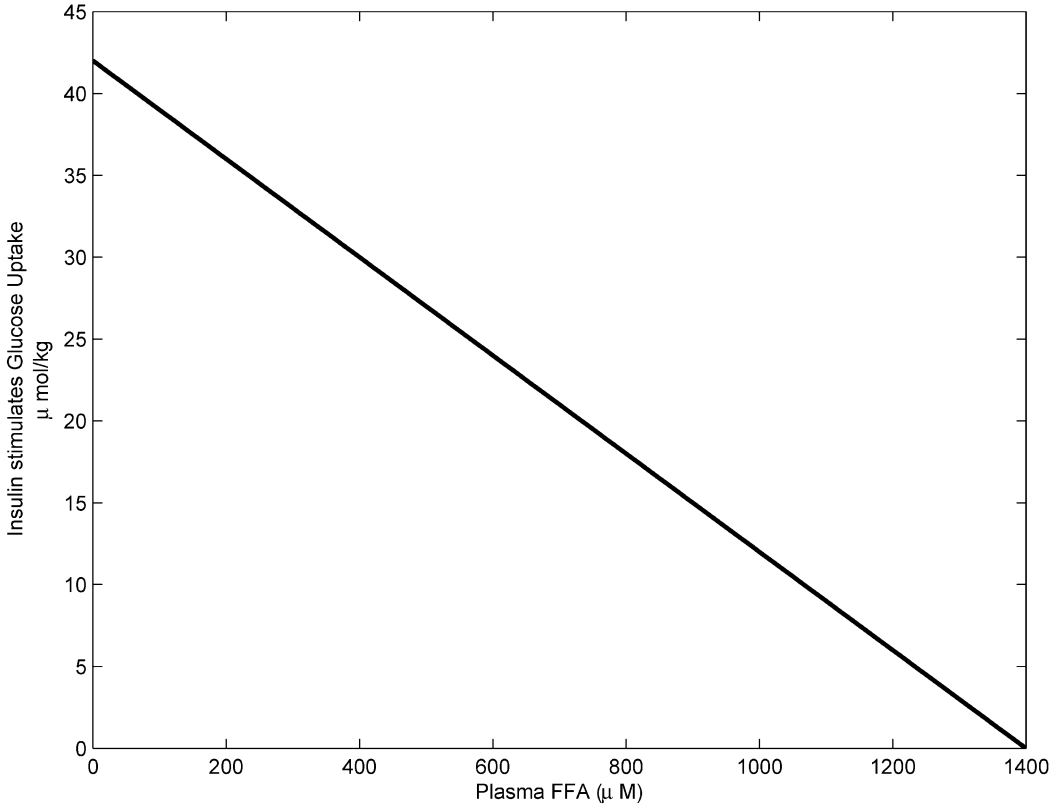

Fig 2 Relationship between insulin stimulated glucose uptake and plasma FFA.

Table 3 Comparison of glucose levels.

time (min)	glucose (normal)	glucose (NIDD)
0	287	392
6	246.6103	368.6992
12	210.2235	341.4574
18	182.2964	315.0566
24	161.6176	298.1958
30	148.8862	273.8715
36	135.3845	252.0832
42	127.3611	235.3905
48	121.6063	222.8449
54	117.5489	211.1449
60	114.76	201.0288
66	112.9109	192.275
72	111.7541	184.6969
78	111.1048	178.1379
84	110.8248	172.4656
90	110.811	167.5676
96	110.9857	163.348
102	111.291	159.7246
108	111.6833	156.6262
114	112.1301	153.991
120	112.6072	151.765

Table 3 continued

time (min)	glucose (normal)	glucose (NIDD)
126	113.0968	149.9009
132	113.5958	148.3566
138	114.0651	147.0923
144	114.5279	146.0704
150	114.9699	145.2568
156	115.3884	144.6212
162	115.7817	144.1372
168	116.1492	144.7819
174	116.491	143.5355
180	116.8074	143.3808

Table 4 Comparison of plasma insulin levels.

time (min)	plasma insulin (normal)	plasma insulin (NIDD)
0	351	1322
6	95.5292	663.8612
12	33.6908	343.5263
18	18.8298	189.3898
24	14.9899	115.9588
30	13.7715	85.8273
36	12.6082	64.7891
42	11.719	56.6519
48	10.865	52.1133
54	10.2328	48.9679
60	10.0573	46.2293
66	10.0141	43.4921
72	10.0034	40.6213
78	10.0008	37.6027
84	10.0002	34.472
90	10.00005	31.2811
96	10.00001	28.0837
102	10	24.9286
108	10	21.8583
114	10	18.9081
120	10	16.1064
126	10	13.4787
132	10	11.7208
138	10	10.8512
144	10	10.421
150	10	10.2082
156	10	10.10303
162	10	10.0509
168	10	10.02521
174	10	10.0124
180	10	10.0061

Table 5 Comparison of remote insulin levels.

time (min)	remote insulin (normal)	remote insulin (NIDD)
0	0	0
6	0.009402	0.009692
12	0.01086	0.01357
18	0.010484	0.014709
24	0.009736	0.014611
30	0.009089	0.014125
36	0.008179	0.013184
42	0.007444	0.012339
48	0.00674	0.01152
54	0.006069	0.010747
60	0.005447	0.010024
66	0.004886	0.009347
72	0.004381	0.008712
78	0.003928	0.00812
84	0.003521	0.007542
90	0.003157	0.006998
96	0.002831	0.006477
102	0.002538	0.005978
108	0.002275	0.005498
114	0.00204	0.005036
120	0.001829	0.004592
126	0.00164	0.004167
132	0.00147	0.003761
138	0.001318	0.00385
144	0.001182	0.003041
150	0.001059	0.00273
156	0.00095	0.002449
162	0.000852	0.002196
168	0.000764	0.001969
174	0.000685	0.001766
180	0.000614	0.001583

Elevated level of plasma FFA and insulin simulated glucose uptake by the cells of the body shows a inverse linear relationship implies that if the level of FFA increases, glucose uptake by the cells decreases [6], as shown in Fig. 2. Total stimulated (insulin stimulated plus basal) glucose uptake has been inhibited by 40–50 % in isoglycemic and in euglycemic patients at plasma FFA concentration of ~950 and ~550 μ M respectively [9], hence the expression $-X(t)G(t)$ in the first equation of the model (1–3) is changed to $-(0.5)X(t)G(t)$. This will lead to a change in the first equation of minimal model. Also as reported by Boden peripheral insulin sensitivity and hence whole insulin sensitivity decreases which is represented by p_3 in Eq. 2. Hence there will be a change in the numerical value of p_3 which will be reflected in the simulation of the modified model. FFA is found to have an affect on peripheral insulin resistance which is represented by p_5 in Eq. 3 and hence we allow the value of parameter p_5 to vary. After making the above discussed changes, the modified mathematical model

for the glucose - insulin dynamics of NIDD people is given below:

$$\frac{dG(t)}{dt} = -(0.5)X(t)G(t) - p_1(G(t) - G_b), G(0) = G_0 \quad (4)$$

$$\frac{dX(t)}{dt} = -p_2 X(t) + p_3(I(t) - I_b), X(0) = X_0 \quad (5)$$

$$\frac{dI(t)}{dt} = -p_4(I(t) - I_b) + p_5(G(t) - G_c)^+ t, I(0) = I_0 + I_b \quad (6)$$

2. Numerical Simulation

On the basis of above results, numerical simulation has been carried out by using Matlab 2012b. Boden suggested that for every 100 μM increase in plasma FFA, peripheral insulin sensitivity decreases by ~8 % [6], and whole insulin sensitivity decreased by approximately 76% in obese people as compared to normal subjects [5]. The value of p_3 in the model (4–6) is taken as 8% of the value p_3 used for normal subjects, hence $p_3 = 0.0000024$, obtained from the relation $S_I = p_3 / p_2$ (insulin sensitivity for normal people) and $S_I' = S_I - 76\ \%\ S_I$ (insulin sensitivity for NIDD people) . FFA could account for maximally 50% of peripheral insulin resistance in patients with type 2 diabetes [6], hence the value of the parameter p_5 in the model (4–6) is 50% more of the value used for normal subjects, therefore $p_5 = 0.0015$ is taken for the numerical simulation. The values of all the parameters for normal and NIDD subjects are given in Table 2.

3. Results

Elevated level of plasma FFA cause decrement in insulin sensitivity and increment in insulin resistance, because of which glucose level does not reach to the normal basal value. This effect on the NIDD people are shown in Fig. 3. Comparison between the changes in glucose and insulin concentration in normal and elevated FFA in NIDD subjects is shown in Fig. 4. Fig. 4(a) depicts that glucose level approaches to physiological basal level faster in normal people than in NIDD with elevated FFA.

It is also observed that more time is taken by NIDD people with elevated FFA than normal to attain nearly same glucose level. The effects of elevated FFA in insulin level can be seen from Fig. 4(b) and 4(c). These figures shows that more insulin is required in NIDD people with elevated FFA to perform the same action compared to normal people.

4. Conclusion and Future Work

The present mathematical model shows that elevated level of plasma FFA inhibit glucose uptake, glucose utilization, decrease insulin sensitivity and increase insulin resistance in NIDD people. It also explained the need of external insulin in NIDD with elevated FFA.

This model can be extended to the inclusion of obesity in terms of BMI (body mass index) through parameters to further explore the effects of obesity and elevated FFA in normal and NIDD people.

Acknowledgement

We acknowledge Delhi Technological University, Delhi for the financial support.

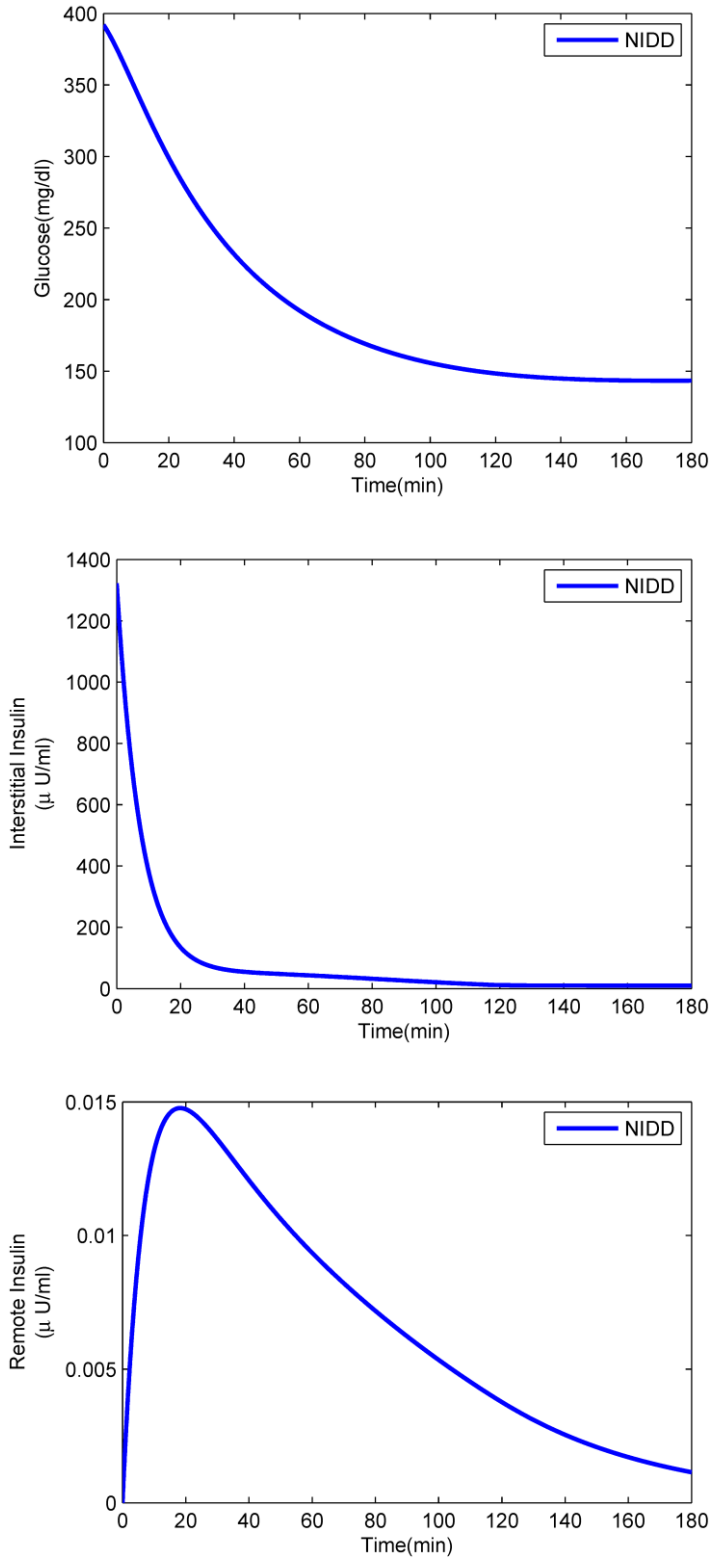

Fig. 3 Glucose - Insulin dynamics for NIDD subjects.

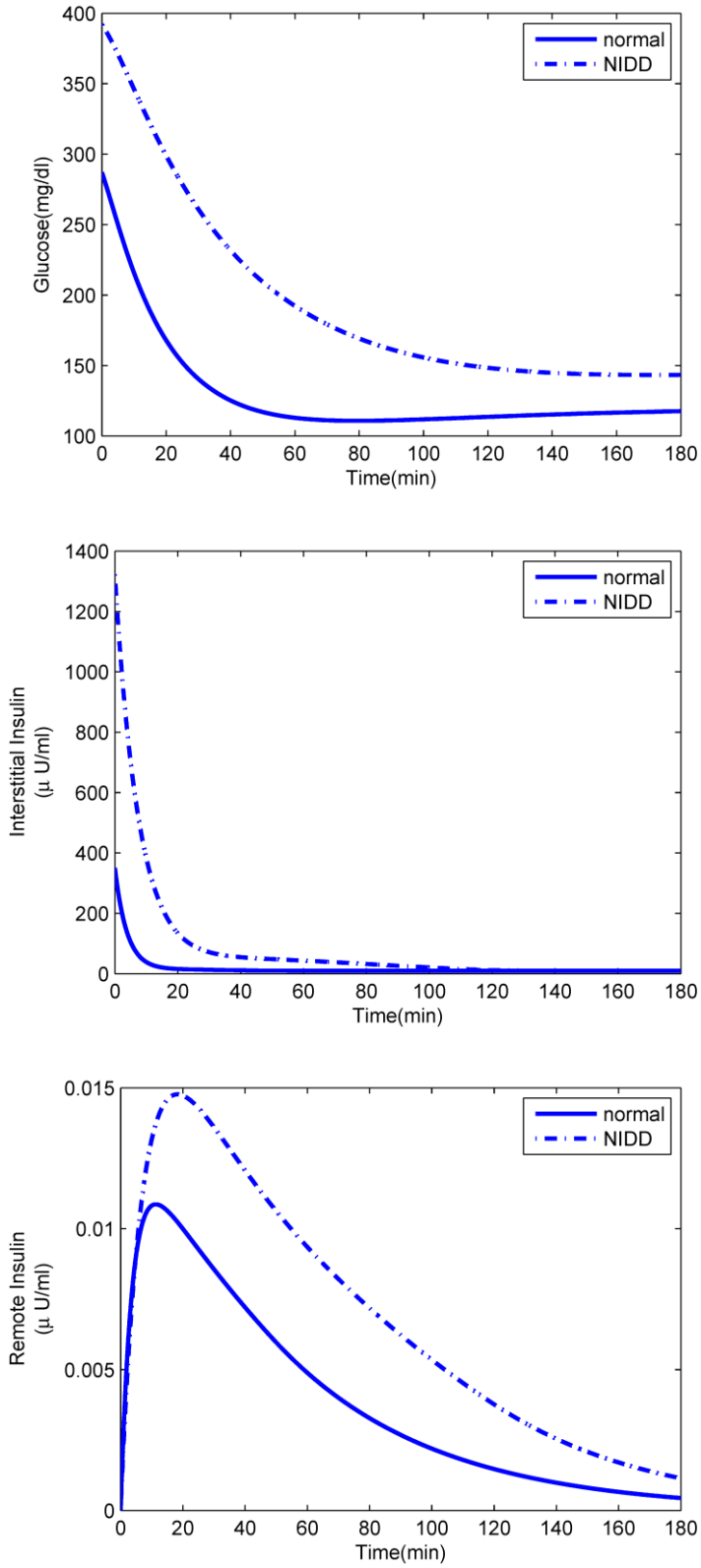

Fig 4 Comparison of glucose - insulin dynamics for normal and NIDD subjects.

References

[1] Boden G (2001) Pathogenesis of Type 2 Diabetes: Insulin Resistance. Endocrinology and Metabolism Clinics of North America. (30):801-815.

[2] Ogden CL, Carroll MD, Curtin LR, et al. (2010) Prevalence of high body mass index in US children and adolescents. 2007-2008. JAMA. (303):242-249.

[3] Santomauro ATMG, Boden G, Silva MER, Rocha DM, Santos RF, Ursich MJM, Strassmann PG, Wajchenberg BL (1999) Overnight Lowering of Free Fatty Acids With Acipimox Improves Insulin Resistance and Glucose Tolerance in Obese Diabetic and Nondiabetic Subjects. Diabetes (48).

[4] Hoffman RM, Boston RC, Stefanovski D, Kronfeld DS, Harris PA (2003) Obesity and diet glucose dynamics and insulin sensitivity in Thoroughbred geldings. J ANIM SCI. (81):2333-2342.

[5] Lee A, Ader M, Bray GA, Bergman RN (1992) Diurnal variation in glucose tolerance, Cyclic suppression of insulin action and insulin secretion in normal-weight, but not obese subjects. Diabetes (41):750-759.

[6] Boden G (1998) Free Fatty acids (FFA): A link between obesity and insulin resistance. Frontiers in Bioscience (3):169-175.

[7] Boden G, Jadali F, White J, Liang Y, Mozzoli M, Coleman E, Smith C (1991) Effects of fat on insulin-stimulated carbohydrate metabolism in normal men. J Clin Invest (88):960-966.

[8] Boden G, Chen X, Ruiz J, White JV, Rossetti L (1994) Mechanisms of fatty acid-induced inhibition of glucose uptake. J. Clin. Invest. (93): 2438-2446.

[9] Boden G and Chen X (1995) Effects of Fat on Glucose Uptake and Utilization in Patients with Non-Insulin-dependent Diabetes. Division of Endocrinology/Metabolism and the General Clinical Research Center. Temple University School of Medicine. Philadelphia. Pennsylvania 19140:1261-1268.

[10] Boden G (1997) Role of fatty acids in the pathogenesis of insulin resistance and NIDDM. Diabetes (46):3–10.

[11] Reaven GM, Hollenbeck C, Jeng CY, Wu MS, Chen YDI (1988) Measurement of Plasma Glucose, Free Fatty Acid, Lactate and Insulin for 24 h in Patients With NIDDM. Diabetes (37).

[12] The NS, Richardson AS, Larsen PG (2012) Timing and Duration of Obesity in Relation to Diabetes. Epidemiology / Health Services Research. Diabetes Care.

[13] Boden G, Cheung P, Stein TP, Kresge K, Mozzoli M (2002) FFA cause hepatic insulin resistance by inhibiting insulin suppression of glycogenolysis. Am J Physiol Endocrinol Metab 283:E12-E19.

[14] Bergman RN, Phillips LS, Cobelli C (1981) Physiologic evaluation of factors controlling glucose tolerance in man: measurement of insulin sensitivity and beta-cell glucose sensitivity from the response to intravenous glucose. J. Clin. Invest 68 (6):1456-1467.

[15] Welch S, Gebhart SS, Bergman RN, Phillips LS (1990) Minimal model analysis of intravenous glucose tolerance test-derived insulin sensitivity in diabetic subjects. J Clin Endocrinol Metab. 71(6):1508-18.

[16] Pacini G and Bergman RN (1986) MINMOD: a computer program to calculate insulin sensitivity and pancreatic responsivity from the frequently sampled intravenous glucose tolerance test. Comput. Methods Programs Biomed (23):113-122.