


The Syndrome of Fasting Hyperglycaemia with Post Prandial Euglycaemia

ASV Prasad*

G.I.T.A.M Dental College, Visakhapatnam,
Andhra Pradesh, India

*Corresponding author: Dr. ASV Prasad

 drasv@ymail.comAsst.Professor (Retd) of Internal Medicine,
G.I.T.A.M Dental College, Visakhapatnam
530045, Andhra Pradesh, India.

Tel: 9849111738

Citation: Prasad ASV (2018) The Syndrome of Fasting Hyperglycaemia with Post Prandial Euglycaemia. J Appl Microbiol Biochem. Vol.2 No.1:3

Abstract

The fully developed syndrome of type 2 diabetes mellitus (DM2), as known to everyone, is characterised by fasting hyperglycaemia and post prandial hyperglycaemia together. Of the two, fasting hyperglycaemia occurring earlier than postprandial hyperglycaemia is also well recognised. It implies that full blown picture of DM2 develops in successive steps. Like-wise there might be some more stages by which DM 2 passes before it is fully established, though they may not be recognised, because of late presentation of patients in the course of development of DM2. This article intends to focus on such an intermediary stage, where the FBS is already high but the post prandial blood sugar (PPBS) is still in euglycaemic stage. The early events in the pathogenesis of DM2 are reviewed as to which out of these factors is responsible for the syndrome under consideration. The relative pros and cons of the earlier suggestions are examined to arrive at the conclusion that, the glucose transporter 2 (GLUT 2) inhibitions is probably the cause of this syndrome. The one explanation could explain fasting hyperglycaemia and GLUT 2 inhibition is traced to increased FFFs (Free Fatty Acids) / induction of B oxidation of fats in DM2.

Keywords: Fasting hyperglycemia; Post prandial euglycaemia; Insulin resistance; First phase insulin secretion; Pulsatile nature of insulin secretion

Received: March 15, 2018; **Accepted:** March 26, 2018; **Published:** April 02, 2018

Introduction

The reporting in literature of the syndrome of fasting hyperglycaemia with post prandial euglycaemia is sparse. The true prevalence / incidence is not known. Late detection, at the stage of established DM2 might be one reason to miss it and uncertainty of significance may be the reason for under reporting. This syndrome is distinct from the Dawn phenomena and Somogyi phenomena, on one hand as having the element of elevated Fasting blood sugar level and on the other hand the idiopathic /reactive post prandial hypoglycaemias which are though captioned as entities with low post prandial blood sugar (PPBS); they are Infact conditions in which the blood sugar levels are at hypoglycaemic level. Whereas in the present reported syndrome the PPBS is in euglycaemic level. The very existence of this syndrome questions the accepted conclusions of some of the studies alluded to below like UK Prospective diet study and Belfast study. Though appearing as naive, the solution to the problem offered, if proved on verification to be correct, not only vindicates the stand taken by the new hypothesis proposed vide infra, but also is simple and keeps medication at bay for at least time being!

Discussion

The established cases of DM2 are characterised by both fasting and post prandial hyperglycaemia. First to appear is the Fasting Hyperglycaemia (FHG), followed by post prandial hyperglycaemia. There is a stage of impaired glucose tolerance or 'pre-diabetic' stage before the established. Conventionally the blood sugar (BS) range between 110 to 125 mg/dl is considered as indicative of pre- diabetes, while FBS above 126 mg/dl is taken as established DM2. Few cases are seen with increased FBS but normal PPBS. This perhaps represents a transitional state before the onset of established DM2. It is also possible to miss this stage due to late presentation of cases of DM2 by which time both FBS and PPBS levels are raised beyond normal range. In any case it also indicates that the pathogenesis of increased FBS and PPBS are different and established diabetes mellitus II evolves sequentially in two stages mainly.

Traditionally the raised FBS is explained by increased endogenous glucose production (EGP) and decreased tissue uptake of glucose. The former results from increased gluconeogenesis (GN) mainly and the later is attributed to the insulin resistance (IR) of the

target organs mainly the liver and skeletal muscle. It is interesting to note that in normal physiological conditions, any addition of sugar to the blood is promptly followed by an appropriate secretion of insulin by pancreas so that the BS level is normalised. This seems to be lost in DM2 as evidenced by persisting raise in FBS due to a defect in early events in insulin secretion. If any increase in BS in normally elicits a surge of insulin, why increase in fasting blood sugar (FBS) due to increased EGP doesn't elicit matching insulin secretion? A close look at the normal physiology of insulin secretion is needed to answer this question. The following events occur whenever there is raise in physiological limits of blood glucose. Glucose is transported into B-cell by GLUT 2. The glucose sensor-the glucokinase, by coupling of glucose to phosphate forms G-6P, which is the first rate limiting step of glycolysis. The glycolysis and oxidative phosphorylation results in production of adenosine triphosphate (ATP). This energy causes membrane depolarisation which causes the closure of voltage gated potassium (K) channels. As a consequence the increased influx of Ca into the cell occurs, leading to Exocytosis of insulin. Before this final step, proinsulin is converted into preinsulin, which is cleaved into insulin and C peptide both of which are secreted by an autocrine mechanism. Dysregulation can occur :

- 1) At the level of GLUT 2;
- 2) Glucose sensing by glucokinase;
- 3) At the level of glycolysis;
- 4) At the level of closure of voltage gated K channels;
- 5) Modulations of intracellular calcium;
- 6) Defective first phase insulin secretion;
- 7) Loss of pulsatile insulin secretion is believed to be involved in the pathogenesis of DM2.

The failure of glucose sensor mechanism by glucokinase vs. GLUT 2 failure

The glucokinase is found to be normal in DM2 glucose flux through glucokinase at basal insulin level is impaired in DM2 [1]. The glucose from the blood is transported by GLUT 2, failure of which is responsible for the non-functional glucokinase sensor mechanism. GLUT 2 is inhibited by increased FFA in blood [2]. The later is a known consequence of increased lipolysis under the influence of glucagon which shifts the energy metabolism from carbohydrate based (glycolysis) to fats (B oxidation). Incidentally the same shift in energy metabolism also explains the increased GN that is responsible for increased FBS as seen in DM2. So, it is reasonable to think that the cause and failure to control increased FBS are due to a single cause, i.e., increased FFA/B-oxidation of fats. It is also known that chronic exposure of B-cells to increased FFA will inhibit the insulin secretion of insulin due to lipotoxicity and also insulin action leading to insulin resistance which is seen to be the advocated cause of persistence of high FBS due to failure of the peripheral utilisation of insulin.

The relative contribution of the failure to secrete insulin due

to GLUT 2 failure and resistance to the secreted insulin is debatable. Insulin resistance may be interpreted as that, insulin is secreted in response to increased FBS, but is ineffective. This interpretation testifies the observed phenomena in DM 2, i.e., 'the hyperinsulinemia' which is explained as pancreatic B cell's effort to overcome the increase in insulin resistance as evidenced by higher and higher levels of FBS, in compensate by producing more and more insulin, ultimately resulting in the observed hyperinsulinemia in DM2. But how the B-cells actually do this increased production is not explained. On the other hand, if GLUT 2 is inhibited how could B cells achieve this increased production? This leads one to doubt whether the increased production or decreased clearance is responsible for persistent hyperinsulinemia. The degradation rates of insulin in diabetics and non-diabetics are said to be not different. It must be remembered that the insulin is degraded not only by the IDE, but also by the internalised functional insulin receptor with subsequent degradation in lysosomes of the target cells. It is perhaps reasonable to suggest that since insulin receptor is non-functional in DM2 due to insulin resistance, the part of insulin that is normally degraded by above said internalised receptor is left out and may contribute to the hyperinsulinemia. This perhaps is the original concept of this author as no reference to it is found in the literature. However this unutilised fraction is responsible for the observed hyperinsulinemia is not known. It must be accepted that the actual mechanism of hyperinsulinemia is far from being clear as the mechanism of the agreed increase in insulin production is not ever questioned nor evidence to that extent is adduced so far. So the last word on the cause of hyperinsulinemia in DM 2 is yet to be said.

The common ground to failure of glucose sensing mechanism due to GLUT 2 failure and hyperinsulinemia is the accepted B cell dysfunction in DM2. The dysfunction may decrease or increase the insulin secretion till the ultimate stage of B cell exhaustion is reached when they no longer secrete insulin. The B cell dysfunction brings us face to face with two associated and accepted phenomena in the pathogenesis of DM2. They are loss of first phase insulin secretion and loss of pulsatile nature of the insulin secretion. The relevance of these two to the present context of increased FBS and normal PPBS remains to be explored. This is so because the PPBS whose pathogenesis is conceded to be different from that of FB, has something to do with it.

It is believed that both the above phenomena occur in the pathogenesis of DM 2 sometime when the position changes from IGT to established DM2 i.e., in the transitory stage in between. Hence already the first part of increased FBS is explained and what remains to be explained is how still the PPBS is normal with FBS raised.

Role of K ATP channels vs. impaired glycolysis in B-cells

Failure of GLUT 2 to transfer glucose into the B-cells and consequent impaired glucokinase sensor mechanism is expected to impair glycolysis in the B-cells. Inhibition of the glycolytic enzymes i.e., the PFK and PDH were suggested by Randle in his

Randle cycle, [3] as early as 1963. This inhibited PFK function lead to the proposal of DOM hypothesis, which trace these defects subsequent events.

The DOM (dual oscillatory mode) hypothesis

Dual Oscillator Model (DOM), consists of a slow metabolic oscillator based on the glycolytic enzyme phosphofructokinase (PFK), and an electrical or ionic oscillator, which is mediated by negative feedback of intracellular free Ca on K-Ca channels and changes in ATP/ADP acting on the ATP-sensitive potassium channels of the beta cell (K ATP channels) [4,5] According to this hypothesis, the cyclic activity of PFK leads to slow oscillations in ATP/ADP, which cyclically regulate KATP channel activity in the beta cell plasma oscillators and action potentials, resulting in the increase in Ca that triggers insulin granule exocytosis. The inhibited PFK in DM2 may explain the closure of K ATP channels and the loss of pulsatile insulin secretion (see below) as per this hypothesis.

The role of intracellular calcium ion oscillations

This pulsatile β -cell secretion pattern is controlled by an intrinsic rhythm of intracellular Ca²⁺ oscillations [6].

First phase insulin secretion

The earliest detectable defect in β -cell function is commonly thought to be a reduction in first-phase insulin release [7] Studies found that first-phase insulin was reduced in individuals with plasma glucose in upper ranges of normal and was essentially absent in people with fasting hyperglycemia [8,9] People with IGT had reduced plasma insulin levels at 30 min after glucose ingestion (first phase insulin secretion) and "normal or increased" plasma insulin levels at 120 min (2nd phase insulin) release [10]. It is not intended to go into the details of these 2 phases of insulin secretion and the readers are advised to consult appropriate sources. The concept that insulin resistance precedes β -cell failure in the progression to type 2-diabetes became widely believed [11] and was considered a hindrance to accepting the loss of first phase insulin secretion as the initiating event. The normal PPBS are considered as an index of intact 'first phase release of the insulin'. Needless to say that when this is lost the PPBS is no longer normal and the second criteria DM2 i.e., the increased PPBS are fulfilled. It is a known fact that insulin response to intravenously administered is lower than that induced via enteric route either as glucose (oral GTT) or food- the so called 'incretin effect'. Also it is seen that even though the EPG induced secretion is resistant to insulin action, the incretin effect still effective. So the first phase insulin action is with respect to food or (oral GTT) is still intact. There is unanimity that first phase insulin is reduced in those with IGT as well as their first degree relatives. In addition they had insulin resistance also. Normal persons with first degree relatives had B cell dysfunction but no insulin resistance. There is debate (as referred to above) as to whether insulin resistance or the B cell dysfunction is the earliest change to appear in DM2. Also out of the two which the genetic determinant first to be manifested in the course of development of DM2.

There are two issues in the literature to be resolved in this

context:

- 1) It is opined that B cell dysfunction compensates and balances the insulin resistance and when the compensation fails, DM2 develops.

The compensation the B cells are known to offer is hyperinsulinemia to get over the insulin resistance. This is a futile attempt and only worsens the situation as hyperinsulinemia is known to increase IR.

- 2) The evidence in literature favours that B cell dysfunction has genetic basis and appears earlier than insulin resistance. findings of the U.K. Prospective Diabetes Study [12] and Belfast Diet Study [13] demonstrating an ~50% reduction in β -cell function at diagnosis of type 2 diabetes and subsequent further deterioration without an associated change in insulin sensitivity.

Under the circumstances of the above said facts, this syndrome under reference, assumes special importance. If the first phase insulin secretion is lost earlier than insulin resistance, the increased FBS of this syndrome which is explained by IR need to be changed to be due to loss of first phase insulin secretion. If that is the case how the preserved function of normal PPBS is explained as is seen in the syndrome under consideration? Increased FBS with normal GTT is a known phenomenon especially in early detected diabetes 2 cases.

Loss of pulsatile nature of insulin secretion

Pulsatility occurs in healthy human subjects [14] and found disturbed pulsatility in subjects with [15] early stages of type 2 diabetes development. β -Cell mass is reduced by approximately 40-65% when patients present with type 2 diabetes. To compensate for decreased β -cell mass, the remaining β -cells produce high levels of insulin, but the pulsatile secretion pattern is modified in that the insulin pulses are markedly attenuated. This altered insulin secretion has several consequences, including effects on the autocrine regulation of insulin secretion, higher plasma levels of uncleaved proinsulin and development of hepatic insulin resistance in both animals and humans. In addition, more insulin seems to escape hepatic retention, leading to elevated peripheral insulin levels. Insulin resistance has partly been ascribed to decreased number and down regulation of insulin receptors with subsequent effects on the intracellular signalling system, including insulin receptor substrate 1 (IRS-1), ISR-2, Aki and Foxo 1 end with the pulsatile infusion. These findings provide the first direct evidence that the loss of pulsatile insulin secretion leads to intrahepatic molecular changes and altered gene expression consistent with the development of hepatic insulin resistance. Moreover, pulsatile insulin administration was accompanied by a modest decrease in plasma glucose levels, whereas both the constant infusion and the type 2 diabetes-mimicking infusion resulted in increased plasma glucose.

Insulin pulsations vs. insulin clearance

Studies of the effects of insulin pulses on hepatic insulin clearance as large amplitude insulin pulses, whether they are experimentally

imposed [16] or secreted endogenously result in more extensive insulin clearance than smaller pulses as demonstrated in dogs rats and humans [16], as discussed below. Recent data [17] have revealed that glucagon can directly contribute to the loss of insulin secretion by stimulating secretion from the liver of kiss peptin, a peptide that inhibits insulin secretion beta-cell electrical activity is dependent on the influx of Ca²⁺ ions [18,19] that its oscillations increase in duty cycle or plateau fraction as glucose increases [20], and that it leads to the rise in beta cell intracellular free Ca²⁺ that drives the periodic exocytosis of insulin from the beta cells [21]. Same objection to one raised in the case of loss of first phase insulin secretion holds good here also. If increased FBS is caused by the loss of pulsatile nature of insulin secretion, how euglycaemia part of the syndrome is explained? In other words, If the damage occurred at increased FBS level itself how can normalcy (euglycaemia) can be expected at a later or subsequent time? Thus the existence of this syndrome is a stumbling block to the either to unquestioned concepts.

Therapeutic application

The proof of pudding is in its eating. The hypothesis advanced indirectly links the increased FBS in DM2 to overnight fasting itself! This is because eating normalises the BS (PPBS). This is attributed to the food stimulated increasing effect which persists even when insulin resistance has began, as evidenced by raised FBS. So, though a fanciful idea, will a snack or two at midnight help prevent the fasting hyperglycemia as seen in this syndrome? A trial costs nothing except the cost of a snack !It must be noted that this solution is suggested on rational already explained, to this particular syndrome under consideration, but not to the fully established DM2 where both FBS and PPBS are both elevated implying the loss already of the first phase insulin action.

Conclusion

The syndrome of fasting hyperglycemia with post prandial euglycaemia is interpreted as an intermediate stage in the final evolution of fully developed DM2 - the guidelines of diagnosis of which are unambiguous. A lid is placed on the controversies of earlier contentions that whether the loss of first phase insulin

secretion or loss of the pulsatile nature of insulin secretion on one hand and Beta cell dysfunction / the insulin resistance is the earlier and primary event [22,23]. It is hypothesised that the earliest change in the chain of events finally leading to insulin secretion, is failure of GLUT 2 sensor mechanism and that the first phase insulin secretion is still effective due to preserved incretin effect following ingestion of food as evidenced by normalisation of PPBS even though FBS is raised. Further both the high FBS and GLUT 2 defect are noth explained by single pathology ie high FFA levels/ B-oxidation [24-35].

Further it is reiterated that this syndrome negates the conclusion of UK prospective diet study and Belfast studies as referred to in the on-going discussion above, which put loss of Beta cell dysfunction as occur in earlier to the development of insulin resistance. Intact, preservation of the first phase insulin action in post prandial state, is brought to fore and basing on this a tentative non-drug therapy of offering a snack at midnight as a solution to the fasting hyperglycemia part of this syndrome, is suggested, though fancible as the idea may appear. It is cautioned that the same might not work when PPBS is also raised, as obviously, first phase insulin action is already lost by that time [24-35].

Declarations

- 1) This is my original article not under consideration for publication elsewhere.
- 2) I am the sole author of this article and there is no conflict of interest.
- 3) This is not funded by any agency.
- 4) No patient consent is necessary.
- 5) I abide by the copyright rules.
- 6) I am the corresponding author.
- 7) No acknowledgements are needed.
- 8) I abide by your peer group policy rules.

Any other declarations will be provided on demand.

References

- 1 Mevorach M, Giacca A, Aharon Y, Hawkins M, Shamon H, et al. (1998) Regulation of endogenous glucose production by glucose per se is impaired in type 2 diabetes mellitus. *J Clin Invest* 102: 744-753.
- 2 Yoshikawa H, Tajiri Y, Sako Y, Hashimoto T, Umeda F, et al. (2001) Effect of free fatty acids on beta-cell functions: a possible involvement of peroxisome proliferator-activated receptors alpha or pancreatic/ duodenal homeobox. *Metabolism* 50: 613-618.
- 3 Randle PJ, Garland PB, Hales CN, Newsholme EA (1963) The glucose fatty-acid cycle. Its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. *Lancet* 1: 785-789.
- 4 Bertram R, Sherman A, Satin LS (2010) Electrical bursting, calcium oscillations and synchronization of pancreatic islets. *Adv Exp Med Biol.* 654: 261-279.
- 5 Bertram R, Sherman A, Satin LS (2007) Metabolic and electrical oscillations: Partners in controlling pulsatile insulin secretion. *Am J Physiol Endocrinol Metab* 293: E890-900.
- 6 Bertram R, Satin LS, Pedersen MG, Luciani DS, Sherman A, et al. (2007) Interaction of glycolysis and mitochondrial respiration in metabolic oscillations of pancreatic islets. *Biophys J* 92: 1544-1555.
- 7 Gylfe E, Grapengiesser E, Hellman B (1991) Propagation of cytoplasmic Ca²⁺ oscillations in clusters of pancreatic beta-cells exposed to glucose. *Cell Calcium* 12: 229-240.
- 8 Cerasi E, Luft R (1967) "What is inherited-What is added" Hypothesis for the pathogenesis of diabetes mellitus. *Diabetes* 16: 615-627.
- 9 Brunzell J, Robertson R, Lerner R, Hazzard W, Ensinnck J, et al. (1976) Relationships between fasting plasma glucose levels and insulin secretion during intravenous glucose tolerance tests. *J Clin Endocrinol Metab* 42: 222-229.

- 10 Kahn C, Soeldner J, Gleason R, Rojas L, Camerini-Davalos R, et al. (1969) Clinical and chemical diabetes in the offspring of diabetic couples. *N Engl J Med* 281: 343-346.
- 11 Gerich JE (1997) Metabolic abnormalities in impaired glucose tolerance. *Metabolism* 46: 40-43.
- 12 Mitrakou A, Kelley D, Mookan M, Veneman T, Pangburn T, et al. (1992) Role of reduced suppression of glucose production and diminished early insulin release in impaired glucose tolerance. *N Engl J Med* 326: 22-29.
- 13 Pillay T, Langlois W, Olefsky J (1995) The genetics of non-insulin-dependent diabetes mellitus. *Adv Genet* 32: 51-98.
- 14 No authors listed (1995) UK Prospective Diabetes Study 16: Overview of 6 year's therapy of type II diabetes: a progressive disease. UK Prospective Diabetes Study Group. *Diabetes* 44: 1249-1258.
- 15 Levy J, Atkinson A, Bell P, McCance D, Hadden D, et al. (1998) Beta-cell deterioration determines the onset and rate of progression of secondary dietary failure in type 2 diabetes mellitus: the 10-year follow-up of the Belfast Diet Study. *Diabet Med* 15: 290-296.
- 16 Lang DA, Matthews DR, Peto J, Turner RC (1979) Cyclic oscillations of basal plasma glucose and insulin concentrations in human beings. *N Engl J Med* 301: 1023-1027.
- 17 Lang DA, Matthews DR, Burnett M, Turner RC (1981) Brief, irregular oscillations of basal plasma insulin and glucose concentrations in diabetic man. *Diabetes* 30: 435-439.
- 18 Matveyenko AV, Veldhuis JD, Butler PC (2008) Adaptations in pulsatile insulin secretion, hepatic insulin clearance, and beta-cell mass to age-related insulin resistance in rats. *Am J Physiol Endocrinol Metab* 295: E832-E841.
- 19 Song WJ, Mondal P, Wolfe A, Alonso LC, Stamateris R, et al. (2014) Glucagon regulates hepatic kisspeptin to impair insulin secretion. *Cell Metab* 19: 667-681.
- 20 Meissner HP, Schmelz H (1974) Membrane potential of beta-cells in pancreatic islets. *Pflüg Arch Eur J Physiol* 351: 195-206.
- 21 Malaisse WJ, Herchuelz A, Devis G, Somers G, Boschero AC, et al. (1978) Regulation of calcium fluxes and their regulatory roles in pancreatic islets. *Ann NY Acad Sci* 307: 562-582.
- 22 Henquin JC (1987) Regulation of insulin by ionic and electrical events in Beta cells. *Horms Res* 27: 168-178.
- 23 Tengholm A, Gylfe E (2009) Oscillatory control of insulin secretion. *Mol Cell Endocrinol* 297: 58-72.
- 24 Orci L, Ravazzola M, Baetens D, Inman L, Amherdt M, et al. (1990) Down-regulation of beta-cell glucose transporters in non-insulin-dependent diabetes may be the cause of diabetic hyperglycemia. *Proc Natl Acad Sci U S A* 87: 9953-9957.
- 25 Fink RI, Wallace P, Brechtel G, Olefsky JM (1992) Evidence that glucose transport is rate-limiting for in-vivo glucose uptake. *Metabolism* 41: 897-902.
- 26 Ohtsubo K, Takamatsu S, Minowa MT, Yoshida A, Takeuchi M, et al. (2005) Dietary and genetic control of glucose transporter 2 glycosylation promotes insulin secretion in suppressing diabetes. *Cell* 123: 1307-1321.
- 27 Stolarczyk E, Gall ML, Even P, Houllier A, Serradas P, et al. (2007) Loss of Sugar Detection by GLUT2 affects glucose homeostasis in mice. *PLoS One* 2: e1288.
- 28 Thorens B, Weir GC, Leahy JL, Lodish HF, Bonner-Weir S, et al. (1990) Reduced expression of the liver/beta-cell glucose transporter isoform in glucose-insensitive pancreatic beta cells of diabetic rats. *Proc Natl Acad Sci USA* 87: 6492-6496.
- 29 Orci L, Unger RH, Ravazzola M (1990) Reduced b-cell glucose transporter in new onset diabetic BB rats. *J Clin Investig* 86: 1615-1622.
- 30 Gremlich S, Bonny C, Waeber G, Thorens B (1997) Elevated NEFA suppresses Glut2 mRNA expression. Fatty acids decrease IDX-1 expression in rat pancreatic islets and reduce GLUT2, glucokinase, insulin and somatostatin levels. *J Biol Chem* 272: 30261-30269.
- 31 Ohtsubo K, Takamatsu S, Minowa MT (2005) Dietary and genetic control of glucose transporter 2 glycosylation promotes insulin secretion in suppressing diabetes. *Cell* 123: 1307.
- 32 Gremlich S, Roduit R, Thorens B (1997) Dexamethasone induces posttranslational degradation of GLUT2 and inhibition of insulin secretion in isolated pancreatic beta cells. comparison with the effects of fatty acids. *J Biol Chem* 272: 3216-3222.
- 33 Kim Y, Iwashita S, Tamura T, Tokuyama K, Suzuki M, et al. (1995) Effect of high-fat diet on the gene expression of pancreatic GLUT2 and glucokinase in rats. *Biochem Biophys Res Commun* 208: 1092-1098.
- 34 Cerf ME (2007) High fat diet modulation of glucose sensing in the beta-cell. *Med Sci Monit* 13: 12-17.
- 35 Reimer MK, Ahrén B (2002) Altered beta-cell distribution of pdx-1 and GLUT-2 after a short-term challenge with a high-fat diet in C57BL/6J mice. *Diabetes* 51: 138-143.