

# Chronic Hypoxia of Islet cell results in Diabetes Mellitus

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*Source:* <http://sci.tech-archive.net/Archive/sci.med.dentistry/2006-02/msg00262.html>

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  - *Date:* 18 Feb 2006 23:34:38 -0800
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Chronic Hypoxia of Islet cell results in Diabetes Mellitus  
The terms of Insulin Resistance/Sensibility should be stopped in use

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Abstract: DM, as a typical modern disease, its root lies in unhealthy habit of dieting and living style. Taking of high calorie food, such as beef and mutton, keeping intemperance, and/or smoking deteriorate blood quality, demonstrated by viscosity of blood, i.e. hemorheology. When the hemorheology of one's blood gets worse the blood stream would be hard to deliver sufficient oxygen to tissue cells around body. When tissues fall in oxygen debt the cells couldn't generate enough energy to meet their biological demand for energy. Body is surly to take reactions to challenge the situation. It has 3 options to take: 1) do its best to supply more oxygen to tissues; 2) supply more of those, such as glucagons, helpful to increase of blood sugar, the primary fuel; 3) increase the secretion of insulin to help cells absorb more fuel in. At the beginning phase of progression to DM, both glucagons and insulin are in the high altitude. However, since hemorheology keeps beyond the body's capability the situation of oxygen debt of tissues have to be on. When the power of both glucagons and insulin keep in balance the sugar level of blood will be in normal at the expense of high level of insulin, so-called insulin resistance. Sugar glycate red blood cell (RBC) to make it loose electrical polarity, as a result RBC aggregates. Meanwhile, high sugar level activates fibrinogen to worsen the hemorheology. In other words, hypoxia elicits high level of blood sugar, and high sugar level in turn promotes hypoxia of tissues. When this relation keeps on glucagons are to override insulin and push the sugar level higher and higher, totally out of control.

However, not all worsened hemorheology results in DM, demonstrated by those suffering hypertension or/and thrombus. This could be explained by the mechanism of secretion of insulin and glucagons. Insulin secretion is dictated by the rate of lactate effluent from  $\beta$  cell islet (Take a look at the thesis made by guys in Manchester U. later at insulin secretion section) The secretion of glucagons is dictated by the stock of ATP and AMP in a islet cell, other than other tissue cells.

As a remark, hypoxia here is about tissue cells in oxygen debt other

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than blood lacking of oxygen. When blood gets less oxygen during pulmonary cycle body is to compensate by increasing pulse, breathing rate, and more of RBC generation.

Background: The research to DM now is so deeply sophisticated that ordinary one has no courage to get in it. Ironically though, the current research could do no more than admitting that DM is incurable. Should we suspect that current research is somewhat deviated from the proper path? Modern medical about DM is unexceptionally based on the two concepts: Insulin Resistance (IR) and Insulin Sensibility (IS).

When anything is good to lowering of sugar level it is read as "increase of IS" while otherwise as "increase of IR". As IR and IS could explain everything that results in increase or decrease of glucose level people are complacent enough not to get into anything behind IR and IS. This me reminds of "ghost" which was used for quite a long time to explain any natural phenomenon which people couldn't comprehend long time ago.

Encouraged by my experience of healing DM patients I dare to explain DM without IR and IS.

Recall at the historical observations

Let's take a look at observations shared commonly by all DM patients.

1. No DM patient has proper hemorheology.

—This is result of enjoying modern life. No one oppose this proposition though no one sticks it out with it. There may be some one claiming cholesterol indicators are more important than hemorheology. The fact is that there we can see occasionally DM patients with proper cholesterol indicators. This implicates that hemorheology is closely related with DM. When hemorheology is not in order tissues wouldn't get enough oxygen. It implicates oxygen may have its part in formation of DM.

2. Blood lactate level of DM is about 3 times that of normal people. As lactate is only metabolite of glycolysis tissues of DM patients undergo severe oxygen debt.

3. Debility is shared by all DM patients. This symptom is observed even after sugar level is normalized, which implicates DM is about more than so called insulin resistance. This also implicates DM patients couldn't generate lasting amount of energy. When oxygen is in debt cells are no way to generate lasting amount of energy.

4. When drinking alcohols DM patients can enjoy short time of normal life, perfectly normal like a healthy man. Alcohols boost hemorheology. This implicates proper hemorheology is perfectly helpful for DM patients. Proper hemorheology can surly deliver rich oxygen to tissues. Can delivery of rich oxygen make sugar level normal?

5. Glucagon level of DM patients is all in high altitude. When glucagons climb up sugar level is definitely going up as glucagons are for mobilization of fuels, right contrary to insulin. It is rationale to say that when glucagons are stronger than insulin sugar level goes up and up.

(—look at this link, <http://www.TaoPanacea.com/Archives/DataE.htm>, which is clinically observed data of lactate ,insulin and glucagons.)

Items of 1, 2, 3, and 4 above all finger at issue of oxygen debt. Could

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DM be direct result of hypoxia of tissues?

It should be noted that hypoxia here is about tissues in debt other than air lacking oxygen. When blood gets oxygen less than enough during pulmonary cycle, like instances in plateau or anemia, body will call up compensation mechanism to makeup the shortage, like increasing rate of pulse and breathing, and/or generating more of RBC. What would the body take when tissues falls in hypoxia?

Glucose is metabolized in two forms in body: Glycolysis to result in 2 molecules of lactate while oxygen is in short; Oxidation to result in 6 molecules of water and carbon dioxide while oxygen is sufficient. It is worth to note that there is great gap between glycolysis and oxidation in terms of energy generation. Glycolysis contributes only 2 ATPs while oxidation 38. Let's think about this scenario.

In a moment, a cell needs 380 ATPs to meet its biological demand. If all these energy is derived by oxidation it needs 10 molecules of glucose and 60 molecules of oxygen to generate 380 ATPs exactly. What if oxygen available is 5% less than enough? As a matter of fact, glycolysis could be the only option to makeup the difference. Let's make a simple calculation. As oxygen available is  $57(60 \times 95\%)$  only 9.5 molecules of glucose could be oxidized. As a result 361 ATPs are generated. To generate another 19 ATPs by glycolysis another 9.5 molecules of glucose has to be put into consumption since one molecule of glucose contributes only 2 ATPs by way of glycolysis. As a result 5% shortage in oxygen results in 19 molecules of glucose in total to generate 380 ATPs which could be delivered merely 10 molecules of glucose when oxygen supply is sufficient. Translated, it is 90% increase in glucose consumption. Would the body meet this big demand? In philosophical view, body will do its best to assist tissues generate enough energy. Body has 3 options to do so.

a) Adjust blood and vessel to make more oxygen permeate through membrane of cells, which is surly impractical at all. So, body has another 2 options to take.

b) Put more fuel, primarily glucose, into blood stream, which could be realized by increasing secretion of glucagons and adrenaline.

c) Assist cells increase efficiency in acquiring glucose, which must be realized by secreting more insulin.

—a, b, and c of above are termed DanTai Effect in whole.

DanTai effect is definitely have the effect of high level of insulin and high level of glucagons with possibly normal level of glucose, which is obviously the reality with people in the beginning phase of progression to DM. In other words, when tissues fall in oxygen debt body calls up DanTai effect. At the beginning phase of progression to DM, the strength of glucagons and insulin is in balance. When this balance doesn't stand sugar level either goes down or up. We discuss the latter case as it is exactly what we call DM. Why the balance between insulin and glucagons loose their ground at last? This is due to mechanism of glucagons secretion.

On the other hand high blood sugar works negatively to oxygen delivery mechanism. High sugar level promotes RBC aggregation by glycation RBC and activates fibrinogen to worsen the hemorheology. Translated, higher blood sugar level boosts more severe hypoxia, as worsened hemorheology

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curtails oxygen transportation, which in turn results in higher blood sugar level. As a result, when this fashion lasts long DM is definitely going to be formed.

The analysis above is plausible in philosophical view, but as observed clinically not all people, such as hypertension patients or thrombus patients, with improper hemorheology gets DM. The reason lies in the mechanisms of insulin secretion and glucagons secretion.

Sure, we expounded etiology of DM without reference to IR or IS. Should we say DM is irrelevant with IS or IR, both of which are descriptive and inclusive terms other than scientific terms.

Mechanisms of insulin and glucagons

Hypertension patients and thrombus patients suffer from worsened hemorheology. However they could escape from claw of DM. Therefore we can conclude worsening of hemorheology not necessarily results in DM.

But DM is most likely result of chronic hypoxia of tissues. Answer to this phenomenon could be found in mechanisms of insulin and glucagons.

Cohort in Manchester U. made a great experiment back in 1989, the thesis of which was published in *Biochem. J.* (1989) 259, 507–511. The thesis could be referenced by this link:

<http://www.TaoPanacea.com/Archives/InsulinSecretion.Pdf>. The statement below is quoted from the thesis:

The secretion of insulin from perfused rat pancreatic islets was stimulated by raising the glucose concentration from 5.6 to 20 mM or by exposure to tolbutamide. The addition of sodium lactate (40 mM) to islets perfused in the presence of glucose (5.6 mM) resulted in a small, transient, rise in the rate of secretion. The subsequent removal of lactate, but not glucose or tolbutamide, from the perfusate produced a dramatic potentiation of insulin release. The rate of efflux of  $^{45}\text{Ca}^{2+}$  was also increased when islets were exposed to a high concentration of glucose or lactate or to tolbutamide, and again subsequently upon withdrawal of lactate. Efflux of  $^{86}\text{Rb}^{+}$  was modestly inhibited upon addition of lactate and markedly enhanced by the subsequent withdrawal of lactate from islets. The output of [ $^{14}\text{C}$ ] lactate from islets incubated in the presence of [ $^{14}\text{C}$ ] glucose increased linearly with increasing concentrations of glucose (1–25 mM). It is proposed that the activation of islets by the addition or withdrawal of lactate is not due to increased oxidative flux, but occurs as a result of the electrogenic passage of lactate ions across the plasma membrane, resulting in islet cell depolarization,  $\text{Ca}^{2+}$  entry and insulin secretion. The production of lactate via the glycolytic pathway, and the subsequent efflux of lactate from the islet cells with concomitant exchange of  $\text{H}^{+}$  for  $\text{Na}^{+}$ , could be a major determinant of depolarization and hence insulin secretion, in response to glucose.

Their conclusion is "The efflux of lactate from the islet cells could be a major determinant of depolarization and hence insulin secretion, in response to glucose". The more fast the lactate is discharged from islet cell the more secretion of insulin is resulted. I term their

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observation as Lactate Theory of Insulin Secretion (LTIS). LTIS could explain neatly about the insulin curves extracted from DM patients, which is still confuses professionals in the field though. DM patient's basal insulin level is about 10% higher than normal people while their insulin level trails far behind that of normal people postprandial (Take a look at <http://www.TaoPanacea.com/Archives/DataE.htm>).

1) DM patients produce far more lactate than normal people in basal condition, about 3 times that of normal people, so it is likely that their islet cells discharge lactate in higher rate, resulting in higher secretion of insulin in basal situation;

2) After meal, normal people undergo steep elevation of glucose level. High level of sugar curtails significantly the delivery of oxygen to islet cells. As a result, big volume of lactate production in islet cells is made, resulting in secretion of insulin 5~6 times their basal insulin level. Since DM patient's sugar level is positioned high even before the meal, therefore glucose elevation is less steep than normal people postprandial, hence the milder change in oxygen delivery, resulting in less steep elevation in lactate production in islet cells.

3) Blood lactate level of DM patients is close to 3 times that of normal people; therefore lactate from islet cells of DM patients is more difficult to come out.

Above 3 reasons explain why DM patient have their insulin level curve far different from that of normal people. We could infer that the longer islet cells suffer from hypoxia the less reactive to sugar level. When this situation goes on, the secretion of insulin could be impaired and glucagons might be in better position.

Let's sit upon the mechanism of glucagons now.

The conventional wisdom tells us ATP/AMP value in tissue dictates secretion of glucagons. As glucagons are secreted by  $\alpha$ -islet cells the proper proposition should be "ATP/AMP value in  $\alpha$ -islet cells dictates secretion of glucagons". When ATP/AMP value goes down, like in the case of  $\alpha$ -islet cells falling in oxygen debt, the secretion of glucagons is promoted. When severity of hypoxia, like in the case of DM, overrides the gain of ATP due to elevation of sugar level the secretion of glucagons becomes rampant. As a result glucagons get upper hand than insulin at last. That's DM.

It should be noted here that in case worsened hemorheology of blood stream is not expressed in vessel web of islet cells both insulin secretion and glucagons should be in order while other parts of body suffer from hypoxia. This is why thrombus or hypertension patients could escape from DM. But it is sure when hemorheology gets worse to a point where islet cells are choked of hypoxia meaningfully DM would be guaranteed. .

There seems other reason as well. We have to note that DanTai effect mobilizes high volume of insulin secretion and glucagons secretion, which is pathological in fact. Can DanTai Effect stay in use without damaging islet cells? The reality is  $\beta$  islet cell is susceptible to damage as clinically demonstrated by many DM patients. When damage is

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suffered more than 85% DM type 1 is realized. When  $\beta$  islet cell get damaged the secretion of insulin is very likely negatively effected. When this damage helps glucagons get upper hand DM is also guaranteed.

The treatment

From elucidations above we can tell DM is result of chronic islet

hypoxia. Accordingly treatment should be for improving delivery oxygen to islet cells. When islet cells get sufficient oxygen the value of ATP/AMP goes up and the secretion of glucagons becomes down and down and gives its way to insulin like in the normal fashion. Meanwhile the secretion of insulin would be close to normal as well and it is great pleasures to human kind were  $\beta$  islet cell could recover bit by bit in this case.

To deliver sufficient oxygen to islet cells, the only practical way is to improve hemorheology of the whole blood system. In fact, the improvement of blood hemorheology results in healing or cure of hypertension, thrombus, and many other cardio-vascular diseases. Therefore treatment of DM is most difficult thing to do. Can there be such magic thing that could help blood get back to its old time happy condition?

Through our great amount of effort and endeavor, we come up with an herbal remedy, Oxygen Booster, which delivers magic result in improving blood hemorheology. We have a measure for efficacy for Oxygen Booster. One should feel fresh in brain and vigorous around the body after taking Oxygen Booster Capsule. As sugar curtails delivery of oxygen DM patients should take bigger dose of Oxygen Booster along with chemical medicine (Metformine the best while one has no weakest liver) or insulin injection. In any case to see the sign of working---fresh brain and vigor in body--- that Oxygen Booster works well is paramount prerequisite. Within 30~60 days after Oxygen Booster delivers efficacy one can get his/her hemorheology normalized.

Oxygen Booster delivers magic result which couldn't be explained by conventional wisdom. This is the direct cause of making new theory of DM etiology come to birth.

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