Hypoxia Plays Key Role in Formation of Both Obesity and Diabetes Mellitus

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Glucose by Nature is a Fuel, oxygen Must be Taken in to Consideration

Obesity and diabetes mellitus are also called metabolic syndrome due to disorder in glucose metabolism. Glucose by nature is a fuel which is to say that its principal mission is to burn itself to provide energy to support the biological need of the body. How can you neglect oxygen when you consider about metabolism of a fuel, unless oxygen supply is always sufficient. In fact, hypoxia is permeated in contemporary world than we usually think. Other than anemia, such factors as erythrocyte flexibility, erythrocyte diameter, and carbonic anhydrase are more likely to bring about hypoxia.

What if the body falls into hypoxia as in made by poor quality of erythrocytes? Without question, hypoxia must cause disorder to glucose metabolism. However, now in clinical practice, hypoxia is almost totally neglected while treating obesity and diabetes. If you are one of the patients, have you ever heard your doctor talking about hypoxia? Isn’t it a serious blunder?

Hypoxia Plays Important Role in Insulin Regulation

Insulin plays pivot role in glucose regulation. The general rule is the more insulin is there, the more quickly a cell takes up glucose from blood, accordingly the faster the sugar level comes down in blood, while the side of glucose supply remains constant. Therefore, The factors that are influential to glucose regulation can do so by affecting secretion of insulin. So, question is how hypoxia affects the secretion of insulin? My proposition is that hypoxia stimulates or promotes insulin secretion. I have two evidences supporting my proposition.

- According to a paper by [1] when people move from sea level to high altitude of 3000m above sea, insulin level increases markedly. Oxygen content of the air at 3000m above sea, is approximately 30% less than that in sea level. It means when you come to high altitude area, your blood carries less amount of oxygen, accordingly all the tissue cells across your body are difficult to acquire oxygen as much as needed. It is an experimental evidence that tells hypoxia stimulates secretion of insulin. Next is theoretical evidence that is more convincing.

- Under hypoxia, cells suffer from energy deficit. In response, cells are designed to do everything to fill up the gap. The alternative is glycolysis, it is fermentation of glucose, where without oxygen, one molecule of glucose contributes 2 ATPs, so-called biological energy currency. In comparison though, the identical one molecule of glucose contributes 38 ATPs under sufficient oxygen supply, that is 19 times of a glucose molecule without oxygen. Assume in a given moment, a cell needs 380 ATPs, it takes 10 molecules of glucose fully oxidized to do the job; However, in case there is 10% of oxygen shortage, to produce the same 380 ATPs, it takes 28 molecules of glucose (9 fully oxidized and extra 19 via glycolysis). 10 glucose molecules over 28, that's net increase of 190% in glucose requirement. In other words, under hypoxia, cells have voracious appetite for glucose in order to fill up the energy gap. How to help cells in hypoxia meet vastly increased demand for glucose? Definitely, high level of insulin. Therefore by design it is mandatory requirement that hypoxia stimulate insulin secretion. Unfortunately, most researches on insulin regulation are without consideration of hypoxia, which is really unthinkable.

So-Called Insulin Resistance can be Resulted from Hypoxia, or Insulin Resistance has Nothing to do with Insulin itself

Insulin resistance is quite popular among both professionals and amateurs. Oddly enough, this concept is absolutely not useful in treating obesity and diabetes. To me, it's one and only role is to give professionals an easy tool to explain with least effort the formation of obesity and diabetes. By consensus, insulin resistance is that cells are less efficient in taking up glucose under the same insulin level. However, in my opinion, so called insulin resistance is probably caused by hypoxia through increasing viscosity, or stickiness, of cytoplasm of tissue cells as viscosity is able to lower the diffusion rate. Under hypoxia, insulin level elevates which in turn helps cells take up increased number of glucose, many of which end up in water soluble metabolic intermediaries other than water and carbon dioxide because the oxygen supply is in shortage. With accumulation of metabolic intermediaries in cytoplasm, intracellular fluid becomes sticky because the more number of water soluble molecules the more sticky is the cytoplasm. Uptake of glucose is of diffusion. According to diffusion law, the more sticky...
is the cytoplasm the more slow is the rate of glucose diffusion. Since glucose enters with lower speed, cells are naturally less efficient in taking up glucose. Therefore, so-called insulin resistance can be made by hypoxia, has nothing to do with insulin itself, is totally useless, and should be deserted.

Fat Cells are Better in Uptake of Glucose than Most other Cell types Under Hypoxia

Obesity is in essence result of fat cells storing too much fat. By design, fat cells are better in uptake of glucose than most other cell types under hypoxia due to two advantages.

- it has second most dense distribution of insulin receptors [2], second only to liver cells. That means fat cells have more chance utilizing insulin to take up more glucose than most other cells
- Fat cells use glucose to make fat, which means most glucose molecules absorbed are not ending up in water soluble metabolic intermediaries, which is good for maintaining lower viscosity. And lower viscosity is a plus for quick uptake of glucose. As a result, under prolonged hypoxia, more and more glucose is taken by fat cells to make fat, and the result is obesity.

Other two Important Factors Affecting Insulin Secretion

There is consensus that sustained high level of insulin, or hyperinsulinemia, causes obesity. High insulin level accelerates uptake of glucose by fat cells which results in obesity. Therefore, to identify all those factors that influence the secretion of insulin is the key to the subject. (Table 1)

First, Hypoxia, as just explained, stimulates insulin secretion, increasing insulin level, which over time causes obesity. We can observe that obese people usually shows hypoxic manifestations, such as less energetic, sleepiness, and so on.

Second, incretin, a hormone secreted by small intestine, is another factor that stimulates insulin secretion, increasing insulin level, which is obviously a plus for formation of obesity. The persuasive example is probably the case of Gastric Bypass Surgery which is reported to be effective in weight management. The surgery excises significant length of small intestine, which, in my opinion, unknowingly lowers incretin secretion, because the excised length of small intestine contains many cells that are capable of secreting incretin. The decrease incretin secretion translates into reduced insulin level, which in turn is most effective for weight management. The interesting part is the surgery by design is not to reduce the number of incretin-secreting cells. The original objective of the surgery was to lower the absorptive capability of digestive tract by means of excising certain length of small intestine. However, my point is that without lowering insulin level any means of weight management wouldn’t work at all. If the insulin level remains high, the hypoglycemia is inevitable shortly after each meal, which induces strong sensation of hunger, and one has to eat whole lot again, no matter how is the absorptive capability of the digestive tract. See those obese people, they have voracious appetite for food, which is the result of hypoglycemia which in turn is caused by high level of insulin. Therefore, for weight management, manipulation of insulin level is the ultimate key, other than the absorptive capability of the digestive tract.

Thirdly, epinephrine, or adrenaline, secreted by adrenal glands, inhibits insulin secretion, lowering insulin level, which causes thinness. High level of epinephrine brings about several other manifestations, such as short temper, hyperactivity, insomnia, et cetera. If you are good on observation, you will find none of these traits is connected to obese people, which implicates that obese people are low in epinephrine. In fact, if anyone is high in epinephrine, they are off from obesity because high level of epinephrine inhibits emergence of high insulin level which is precondition for the formation of obesity.

Formation of Diabetes M

By definition, diabetes is the situation where sugar level maintains at higher than normal level. For regulation of glucose, there are always two sides in work, the side of glucose uptake by tissue cells and the side of glucose supply, mainly by the liver. We should be very clear that while the rate of glucose supply exceeds the rate of glucose uptake, sugar level is doomed to elevate, and the formation of diabetes is unavoidable. The rate of glucose uptake is decided by the insulin level which just like we have discussed above that 3 factors work on in concert. So we have to consider all of them altogether. What about the rate of glucose supply? Similarly it is decided by levels of two hormones, epinephrine and glucagon. The higher level of either of the two, the more quickly liver supplies glucose to the blood.

Obviously, to achieve the diabetes where glucose supply exceeds glucose uptake, there are only 2 scenarios. One, high rate glucose uptake combined with higher glucose supply; and the other, low rate of glucose uptake combined with high rate glucose supply.

Scenario 1: Type 2 Diabetes, High Rate of Glucose Uptake Combined with Higher Rate of Glucose Supply

Type 2 diabetes is characterized by obesity, being less energetic, high blood pressure, and susceptibility to hunger. Obesity implicates high level of insulin which causes high rate of glucose uptake. Question: What brings about high level of insulin? We should consider all 3 factors that influence insulin secretion, one by one.

<table>
<thead>
<tr>
<th>Hypoxia</th>
<th>Poor RBC quality or Microcirculation disturbance</th>
<th>Stimulates insulin secretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incretin</td>
<td>Small intestine</td>
<td>Stimulates insulin secretion</td>
</tr>
<tr>
<td>Epinephrine(Adrenaline)</td>
<td>Adrenal glands</td>
<td>Inhibits insulin secretion</td>
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First hypoxia, which stimulates insulin secretion. Obesity is characterized by being less energetic, which exactly tells they are hypoxic.

Second, epinephrine must be at low level because it inhibits insulin secretion. Short temper is most prominent manifestation of high level epinephrine. And obese people are rarely in short temper, which implicates they are in low level of epinephrine.

Thirdly, It is not sure how is incretin secretion with obesity, but one thing is sure that low level of incretin drags down insulin level. Therefore, presumably the level of incretin is normal or higher than normal with type 2 diabetes.

High level of insulin helps tissue cells take up glucose quickly, causing low glucose level, or hypoglycemia, shortly after each meal. Hypoglycemia induces strong sensation of hunger, that's the reason of susceptibility to hunger with obesity and type 2 diabetes. Severe hypoxia is able to cause high blood pressure, mechanism of which is supposedly like this: While brain is in short supply of oxygen, our body is designed to whip the heart to pump out more blood, which obviously elevates blood pressure.

Therefore, all characteristics of obesity and type 2 diabetes, such as being less energetic, susceptible to hunger, and hypertension, are rooted in hypoxia.

Next, the side of glucose supply, "higher rate glucose supply", which involves liver releasing glucose at higher rate to the blood.

By analogy, liver is like the oil tank of a car, and the glucose is like oil. After each meal, liver builds up glucose reserve, which is like filling up the oil tank. The fact that obese people or type 2 diabetes are susceptible to falling in strong sensation of hunger shortly after each meal implicates liver is depleted of glucose very quickly, no longer able to replenish the blood of sugar. To do so, high level of glucagon or high level of epinephrine is required. But we concluded above that obesity and type 2 diabetes is impossible to have high level of epinephrine. Therefore the only possibility on table is high level of glucagon, which stimulates liver to quickly release glucose.

Therefore it is reasonable to assume that hypoxia may stimulate glucagon secretion by islet A cells which are responsible for synthesis and release of glucagon.

To summarize, under hypoxia, on one hand, insulin level is high which promotes the glucose uptake and causes obesity; on the other hand, under hypoxia, glucagon level is also high which stimulates liver to release glucose quickly, inducing strong sensation of hunger shortly after meal when the liver runs out of glucose reserve. But so far, the side of glucose uptake and the side of glucose supply are in balance both at high rate. How can the side of glucose supply gain upper hand over the side of glucose uptake to give rise to diabetes? We can find the answer still in hypoxia.

Hypoxia over time causes the death of islet B cells which is responsible for insulin synthesis and release, because B cells are by design very susceptible to hypoxia (Low expression of LDH plus high expression of m GPDH) [3]. With increase in death of islet B cells under hypoxia, over time, insulin secretion tapers off. On the other hand, glucagon secretion by islet A cells is not compromised by hypoxia. Therefore, under hypoxia, over time, insulin secretion tapers off, which means the rate of glucose uptake is compromised, while glucagon secretion remains strong, which means the rate of glucose supply remains high. This situation must evolve into diabetes. It is important to note, at the beginning stage, patients of type 2 diabetes are still higher in insulin level than the normal people, but glucagon level is higher. And it is predictable that at the advanced stage, when the number of surviving B cells is too low, the insulin level may dip less than that of normal people, then one is to become thinner day by day. Assume islet B cells don't die under hypoxia condition, then there will be only obesity, and no diabetes at all.

**Scenario 2: (Not Type 1 Diabetes) Low Rate of Glucose Uptake Combined with High Rate of Glucose Supply**

Type 1 diabetes fits into this scenario as well, but is saved of discussion in this article. Here I am talking about a novel type of diabetes, characterized by high level of epinephrine.

In my past 11 years of doing research in hypoxia, I observed that one type of diabetes is quite prevalent, but seems not covered medically. This type of diabetes is characterized by short temper, not necessarily young of age, normal blood pressure, getting thinner day by day upon initiation of the diabetes. Many of them got the diabetes after emotional trauma, which implicates probably there is an issue of microcirculation disturbance in certain region of the brain. Before initiation of this type of diabetes, one may be obese, but upon onset, one gets thinner day by day. Thinning is an important feature, that implicates the patients are low in insulin level, which means the rate of glucose uptake is low. Let's see how the 3 factors that are influential to insulin secretion work together to maintain low level of insulin.

First, Epinephrine is the only hormone that inhibits insulin secretion, therefore the high level of epinephrine is a must for the possibility of low level insulin. This type of patients are characterized by short temper that is exactly characteristic manifestation of high level of epinephrine. But the level of epinephrine should be moderately high given the normal blood pressure of this type of diabetes, because extremely high epinephrine level is likely to cause diastolic hypertension by excessively constricting peripheral vessels, as observed in the scenario of chromaffin tumor, which of course can single-handedly induce diabetes as well.

Second, what about hypoxia which stimulates insulin secretion. To achieve low level of insulin there wouldn't be hypoxia. Epinephrine is a potent agent for increasing erythrocyte flexibility [4] which improves oxygen delivery efficiency of blood, therefore hypoxia is usually off the table under high level of epinephrine. Good oxygen delivery efficiency of blood is also helpful to maintain a normal blood pressure as long as the level of epinephrine is moderately high.

Thirdly, what about the incretin which stimulates insulin? I am not sure how is the incretin secretion. But I suppose incretin level should be normal or low because it stimulates insulin secretion.
Therefore, moderately high level of epinephrine is good enough to achieve low rate of glucose uptake by lowering insulin level, which results in thinness. What about the rate of glucose supply? Epinephrine is a potent agent to stimulate liver to release glucose reserve. Epinephrine also stimulates glucagon secretion by islet A cells [5]. Epinephrine also stimulates fat cells release fat reserve to provide raw material for gluconeogenesis at liver. Therefore, moderately high level of epinephrine is strong enough to boost glucose supply.

Low rate of glucose uptake, combined with high rate glucose supply, the result is surely diabetes. This type of diabetes is in essence result of high level of epinephrine, which is likely caused by microcirculation disturbance in either hypothalamus which regulates secretion of epinephrine at adrenal glands, or simply adrenal glands themselves, which are responsible for synthesis and release of epinephrine.

For such epinephrine-rich diabetes, the solution to microcirculation disturbance is supposedly useful. It is expected that healing crisis is likely to happen at the beginning stage, which means temporary rise in sugar level.

Obviously, it is important to do more research on how incretin and epinephrine is regulated, verifying if they are affected by hypoxia or by what other factors.

References


