


Diabetic Processes are Potentially Reversible

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Abbreviations: DMAFs: diabetes mellitus all forms; HLGB axis: heart, lung, gastrointestinal tract, and brain axis; NHLC: neuronal, hormonal, lymphatic circulations; BLEC: blood lymphatic electrolytes combination; GPs: general practitioners

Diabetes mellitus all forms (DMAFs) could be said to be a metabolic syndrome with and without obesity-associated bloated disease, neuronal stress, and chronically pathophysiologic disorder - a kind of accumulation disease associated with mainly dysfunctional glucose, insulin, and fat metabolism diseases which might become a popular disease combination number 1, soon.

DMAFs are not only a simple metabolic disorder that affects the lives of different subjects significantly and increases mortality and morbidity rates when too late diagnosed, but also are “clinical and laboratories’ failure indicating-end results” concerning National Health status. Consequently, one should make a very long description of DMAFs, which unfortunately are not defined yet, appropriately. Untreated or poorly treated diabetes accounts for approximately 1.5 million deaths per year [1]. The U.S. Centers for Disease Control and Prevention indicates that about 79 million American adults over the age of 20 have prediabetes. An estimated 30–40 million Americans have diabetes, a disease in which there is too much sugar in the bloodstream. Between 7–10 million of them, however, have not yet been diagnosed with the disease. The number of adults with diabetes in the world has increased from 108 million in 1980 to 422 million in 2014 due to a rise in prevalence, population growth, and aging [1]. Diabetes mellitus has been projected to become the 7th leading cause of death in 2030 [1, 2]. It has been estimated that the direct medical costs of diabetes to the world are more than the United States > 827 million dollars [2]. If we look at different developed countries, almost half of the USA and Dutch population is overweight now, and almost one to six are even seriously overweight in The Netherlands. That means too much fat storage, especially belly fat, blown up unhealthy either subcutaneous or visceral fat. Recall in human fat tissue hundreds of types of hormones are produced, and essentially each second after any noxious stimuli communicate with the different vital organs like the heart, lung, gastrointestinal tract, and brain axis (HLGB axis) in a bidirectional positive and negative feedback via neuronal, hormonal, lymphatic circulations (NHLC).

If a subject has too much subcutaneous and/or visceral fat, his/her fat tissue will literally get sick, just like the brain, heart, or liver. An interesting question is whether increasing in physical vast tissue with fat-associated products can affect the body's circulating fluids *i.e.*, blood lymphatic electrolytes combination (BLEC), and gas exchange *i.e.*, oxygenation of different tissue, especially lung alveoli respiration system. Amazingly is well true that any form of DMAFs can affect HLGB, NHLG, and BLEC systems in less than a few seconds. Subsequently, rapid physical changes (temperature, volume, pressure, time) significantly affects (ir-)responsiveness and (ir-)reversibility of the body's complex biological cellular and molecular systems, which are so complex processes that still nobody can prevent it in less than a minute after diagnosis.

Whether it's possible to reverse the DMAFs even for a day, week, month, and/or more than 5 years is a very intriguing and challenging question after 2023 and the next 50 years. Some chronic metabolic diseases could be restored by surgical approaches like fat deposition externally, but whether internal visceral fat deposition could also be surgically restored is still also a big challenge for plastic surgeons. Recently, one is observing many reported positive and negative bariatric surgery results globally.

What do we know about the DMAFs? is generally a group of common endocrine diseases characterized by sustained high blood sugar levels, simultaneously with different disorders in insulin hormone metabolism and functionality issues. Although other hormonal, neuronal, and functional factors are chronically affected as well. In the DMAFs subjects, this is due to either the pancreas not producing enough insulin or the cells of the body not responding properly to the insulin produced, [3–11] increasing BLEC-dependent disorders eventually. If DMAFs patients are left untreated, collateral damage and side effects of too much glucose lead to many health complications *i.e.*, platelets hyper-and/or hypo-activities, which both are very dangerous progression when chronically prolonged [4–6]. Whether a diabetes patient could be clinically supported in such a way that does not need any medicinal/therapeutic management is a big desired wish of any DMAFs, who are suffering from chronic insulin injection, drug usage, obesity discomfort, and an increased morbidity/mortality risk. Up to now, three potential solutions are introduced 1) An extravagant certain diet (regiments) might increase rapid losing weight by more than 15 kg and/or prevent BLECs pathologic changes; 2) Bariatric surgery, which removes physical input and -stimulants directly; 3) Auricular therapies might restore neuronal-vasovagal stimulation, however [4].

It is well-established that prediabetes is reversible [8–13], but it is unclear whether diabetes is reversible once it has been diagnosed. Though, what we don't know is why in different DMAFs' patients the diagnosis and treatments have been applied at a late stage. Which factors and biomarkers are better to choose except those now available to (pro-) diagnose routinely, correctly, and timely? How and why acute and chronic DMAFs could be under/over-estimated in clinical chemistry and hematology practices? Does everybody still look at the wrong picture? Why side effects and collateral damages of different DMAFs indications are not profound enough for random general practitioners (GPs)? Whether underestimation of certain indications by GPs is the main cause? Or know-how is still missing over changes in the BLEC by GPs?

Of interest is whether DMAFs associated-disorders in different hormonal production, cause (ir-)reversible miscommunication between HLGB axis, BLEC changes, and potentially tissue collateral damages have a reversible or irreversible character, clinically. One sincere question remains "Why were different platelets (ir)responsiveness and hypo-hyperactivities measured/reported, in the different DMAFs patient? Why human blood platelets do react to hyperglycemia conditions differently? [4–6] Inconsistent platelets reaction either hyperactivity or hypo-activity in certain groups of DMAFs' patients despite their diabetic background were observed to be the same *i.e.*, all diabetes mellitus type 2 patients. There are big missing links and regrettably (with all due respect) know-how still missing, which are both affecting DMAFs' patients' morbidity and mortality rates, however.

The UK's Diabetes Organization [2] confirmed that the strongest evidence (we have at this moment) suggests that type 2 diabetes is mainly put into remission by weight loss. Remission is more likely if you lose weight as soon as possible after the DMAFs diagnosis is confirmed. However, we do know of people who have put their diabetes into remission 25 years after diagnosis. It's important to know that not everyone who loses this much weight will be able

to put their diabetes into remission [2]. Nonetheless losing 15 kg comes with a lot of health benefits, even if you don't lead to remission. Losing extra weight can lead to fewer medications, and better blood sugar level control, a condition that decreases the risk of BLEC complications. The UK's Diabetes Organization suggested that they don't call that diabetes could be a reversal because this might sound like it's permanent, and there's no guarantee that the subject's diabetes has gone forever [2]. If low-grade inflammation does not occur, many (pro-) inflammatory substances are also not produced/released in a pathologic manner against BLEC. This could be a life-changing approach, and desirable indeed.

There are different causes initiating different DMAFs. Subsequently, medical researchers have not yet discovered how exactly DMAFs could ultimately be prevented in a premature stadium. Well, different scientists believe that prolonged storage of too much fat(-tissue) deposition in the liver, pancreas, and/or another organ affects BLECs, but how type 2 diabetes develops and losing this fat can help put their diabetes into remission in a golden standard protocol is also not agreed globally.

Some people have lost a substantial amount of weight while putting their diabetes into remission through changes severely *via* either an adjustment of their lifestyle, a restricted diet regimen, or by having (> 15 kg) weight loss bariatric surgery are big steps toward a standard clinical solution but not ultimate solution of DMAFs, astutely. Bias is surgical operation not-fit-for-all principle plus side effects, and collateral damage risk is still too high, which prevents one solution-fit- for all.

There are a lot of different ways to lose weight, and there's no one-size-fits-all diet [2]. Gary Yee Ang 2021 reviewed different DMAFs research studies and suggested that prediabetes is reversible, but it is unclear whether all DMAFs are also reversible once it has been diagnosed [3]. The current evidence for bariatric surgery is stronger than intensive medical management, and the presented pieces of evidence are selectively stronger for type 2 compared with type 1 diabetes patients. It is also unclear whether non-obese DMAFs would benefit from such interventions and whether the duration of diabetes before DMAFs becomes irreversible. Further research is needed in this area, especially concerning the subgroup of DMAFs patient who will benefit from surgical interventions. Furthermore, the long-term safety and efficacy remain unknown, especially with arbitrary approaches in intensive medical management [2–4].

Those with insulin resistance, short duration of diabetes, and resistant obesity need more complex pathophysiological attention than DMAFs in the early stages. Further, whether auricular therapies could save DMAFs either temporarily or permanently is not yet elucidated as well completely. Just too soon to conclusively could be said that auricular therapies can offer extra tools to prevent DMAFs progressions because of limited data on cases reported [4]. Whether insulin dependency or independency here in-between plays any pivotal role during auricular therapies was not investigated appropriately. The most important hypothesis is how insulin (in-)dependency could be ignored during and/or after certain treatments of DMAFs were diagnosed. How? and why DMAFs patients initiate different platelets' responses when the whole BLECs balance is pathologically changed chronically is also not a known aspect.

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