# T2DM and the Gut Microbiota

Type 2 Diabetes Mellitus (T2DM) affects over 9% of the United States population alone, constitutes a cause for ensuing cardiovascular disease, and is typically closely linked to obesity status. While obesity has long been perceived to stem from a sedentary lifestyle and high fat intake there is increasing evidence supporting the idea that this is a more complex issue than initially thought. The human gut microbiome has been a recent point of investigation due to the idea that it may be closely linked to T2DM. The aforementioned high fat diets can impact the gut microbiome in a significant way, altering the demography of the gut's microflora, hence shifting the gut into a state of dysbiosis. Dysbiosis is a state that favors the initiation of a cascade inducing metabolic deregulation, increasing inflammation and insulin resistance systemically. Below the relationship of the microbiome to T2DM is briefly discussed.

## 1. Introduction

Diabetes Mellitus (from Greek: "διαβαίνω" (diaveno: to go/cross through) and "μέλιτος" (mel(l)itos: of honey/sweet) in reference to the pass through of glucose into the urine which was the way to diagnose diabetes by ancient Greek physician and father of medicine Hippocrates of Kos, is a disease of uncontrolled hyperglycemia. The term microbiome arises from the Greek "μικρο" – micro meaning "small" (in mathematics and sciences designated with the Greek letter μ ($10^{-6}$) and "βίωμα" – biome meaning "of life". Prior to 2001, the term microbiome was in use, mostly to infer a rather small significantly complex ecological niche incorporating plant and animal life. In 2001, the term "microbiome" was re-discovered, re-surfaced and was used by Nobel laureate-microbiologist Joshua Lederberg to signify the microbial life in symbiosis (under normal healthy conditions) with the human body. Microbiota on the other hand, which is used similarly to the term microbiome, refers to an "ecological community of commensal, symbiotic and pathogenic microorganisms found in all multicellular organisms studied to date from plants and animals". New insights have recently revealed a potential association between the bacterial demography of gut microbes as a mediator on the risk of T2DM and ensuing CVD. While the mechanistic details remain elusive, *in vivo* and human work clearly suggest a link between microbiome and the risk of chronic diseases involving oxidative stress, inflammation and immune response.

It is estimated that 39.8% of the United States population is considered obese, as defined by body mass index (BMI) > 30.0[1][21]. Unhealthy, often hypercaloric diets often combined with sedentary lifestyles are often considered major contributors to the development of the obesity epidemic. Over time, obesity can contribute to the development of disease, including Type 2 Diabetes Mellitus (T2DM). While obesity has long been considered a consequence of lifestyle, there is evidence to suggest that a significant component of obesity may be within a person's own gut. Recent research on the human gut microbiome supports the idea that a person's gut microbiome could, in fact, contribute to obesity, leading to elevated inflammation, insulin resistance, and increasing T2DM risk.

In healthy individuals, the gut microbiota exists in a state of eubiosis, meaning a good and healthy gut profile. Eubiosis (from Greek ευ/eu: good and βίος/bios: life) refers to the normal/healthy profile of gut microflora, as opposed to dysbiosis (from Greek δυς/dys: non-favorable/difficult and βίος/bios: life) which produces a demography that induces risk for certain diseases. In a state of eubiosis the bacterial demography of the gut is comprised primarily of two phyla of bacteria namely Bacteroidetes and Firmicutes, which, in eubiosis, exist at a ratio of 95% Bacteroidetes and 5% Firmicutes[2][21]. Within the gut, both phyla function to degrade dietary fibers and fructooligosaccharides that are otherwise undigestible by humans. This then results in the generation of short chain fatty acids (SCFAs), which can constitute a significant source of energy for humans. It is supported that Bacteroidetes result in SCFA generation in healthy individuals, while in obese individuals, elevated numbers of Firmicutes are observed instead, and seemingly Firmicutes degrade energy yielding compounds[3] in place of Bacteroidetes in obese individuals as well as individuals on poor diets. Such condition in turn results in an excess of Firmicutes within the gut hence leading to increased energy uptake by the host, subsequently inducing higher caloric

bioavailability, positive energy balance, and eventually weight gain[3]. Such excess of Firmicutes is referred to as dysbiosis, defined as any change in the normal or desirable flora in an otherwise healthy gut[2]. Dysbiosis within the gut typically has a negative effect, leading to obesity and the onset of T2DM.

## 2. Metabolic Contributors to Microbiome Profile Demography

SCFAs play an important role within the gut, where they function to line the epithelium and form tight junctions between cells, preventing intestinal permeability[4]. When the B/F ratio is altered, the proteins that form these junctions are reduced, resulting in lipopolysaccharide translocation and the activation of the inflammatory response. It has been demonstrated in several cases that the presence of SCFAs, whether through supplementation or through an ideal microbiome status, reduces insulin resistance and subsequently, the risk of T2DM[5][6][7][8].

Branched chain amino acids (BCAAs) comprise a class of essential amino acids whose elevated levels have been observed in obese individuals and individuals diagnosed with T2DM[9]. Arguably, BCAAs can interfere with insulin signaling, increasing diabetes risk. Elevated BCAA levels have been linked to eventual T2DM diagnosis, while *in vivo* work with rats fed a high fat diet with BCAA supplementation demonstrated increased insulin resistance[9][10].

## 3. Dysbiosis and T2DM Development

T2DM develops when the pancreas is forced to produce gradually increasing amounts of insulin to achieve postprandial glucose clearance, reaching a point of such low insulin responsiveness that normoglycemia cannot be attained[11]. While the exact mechanism is not known, many factors contribute to the development of T2DM, including microbiome health. In a study with 345 Chinese individuals, 60,000 T2DM associated markers were validated, correlating with gut dysbiosis[12]. These markers highlight a strong link between gut dysbiosis and T2DM onset.

Inflammation is one of the first steps associated with T2DM onset. In obese individuals, it has been consistently observed that the expression of pro-inflammatory cytokines is often followed by insulin resistance[13]. Due to these observations, inflammation and the microbiome have been of focus when considering causes and treatments of T2DM. In several studies assessing high fat diets versus inflammatory biomarkers, it has been observed that lower BMIs correlate with a less inflamed state[14], and that changes within the microbiome associated with lower BMI's can actually significantly reduce the inflammatory response[15], suggesting that optimal microbiota can attenuate inflammatory responses.

While insulin resistance eventually leads to T2DM, there is significant evidence supporting the idea that microbiome dysbiosis influences resistance development in terms of its rate of progression. Inoculation of men with metabolic syndrome with microbiota from lean donors resulted in increased insulin sensitivity, and a closer to ideal B/F ratio[16][17]. While the direct connection between insulin resistance and the microbiome is not entirely elucidated, findings begin to provide a foundation for understanding this relationship.

Oxidative stress results from the excess of reactive oxygen species, where an individual has an ineffective antioxidant defense[18]. This is commonly seen in individuals with sedentary lifestyles and high fat intake. Oxidative stress induces inflammation, which in turn increases T2DM risk[19]. It has been seen that in the microbiome of mice with low levels of Firmicutes, oxidative stress was decreased in comparison to mice with high numbers of Firmicutes (from a high fat diet) [18]. Therefore, an optimum B/F ratio is also suggested in the context of oxidative stress as a way to decrease T2DM risk.

## 4. Concluding Remarks

There is strong evidence supporting an association between the microbiome status and T2DM onset, with several aspects of the microbiome health possibly influencing disease development. Microbiomes of T2DM individuals vary greatly from non-T2DM individuals. Diet has been shown to play a significant role in gut health, and a healthy gut is responsible for regulating indirectly many pathways within the body. In the case of dysbiosis, metabolic pathways are regulated sub optimally, effectively increasing obesity and T2DM risk. There is evidence supporting the idea that a plant-based diet may increase the B/F ratio in a more optimal way as well[20][21]. Diet emerges as a key driving factor regarding the establishment of a desirable B/F ratio, and therefore must be considered when discussing the microbiome and obesity risk. Manipulation of the B/F ratio may provide a means to decrease tendency towards obesity, reduce insulin resistance, and reduce the risk of T2DM.

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