Review Article
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Autonomic, immunological and endocrine influences on adipose tissue as an organ

Abstract

White Adipose Tissue (WAT) is typically regarded as a passive storage deposit of excess fat. However, recent research suggests that WAT behaves like an organ system that interacts with the autonomous nervous, endocrinological and immunological systems. Therefore, it is possible that WAT acts as a regulatory organ that keeps the body in homeostasis. This cross-sectional study uses physiological data from 30 patients at the Pinewood Natural Health Centre in Toronto, Canada to derive a description of the role of WAT in the mediation of homeostasis. Statistical methods derive a formula describing the dynamic congruence that contributes to a systems medicine (SM) understanding of the organism. Multiple variables including body parameters, composition, and metabolism, heart rate variability and the immune, autonomous, neural, and endocrinologicial systems were measured and correlated using multiple regression analysis. The null hypothesis was that no variables would correlate; the alternative hypothesis was that at least two variables that would correlate with each other to demonstrate congruence and order. This analysis found strong correlations with parameters of the immune system and metabolism and few correlations with the autonomous nervous system. This suggests that despite the body's complexity, not all systems may contribute equally strongly to overall homeostasis.

Keywords: clinical research, biomedical model, endocrine function, homeostasis, mathematical formula, homeostasis

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Abbreviations: AT, adipose tissue; ATP, adenosine triphosphate; BAT, brown adipose tissue; BeAT, beige adipose tissue; BMI, body mass index; BMR, basal metabolic rate, C/EBP-β); CCAAT, enhancer binding protein beta; DNA, deoxyribonucleic acid; HDP, high-density protein; HSL, hormone-sensitive lipase; LDL, low-density lipoprotein; MYF5, myogenic factor 5; myod myoblast determination protein 1; NADH, nicotinamide adenine dinucleotide (NAD)+hydrogen (H); NK, natural killer; PSNS, parasympathetic nervous system; PPAR-γ peroxisome proliferator-activated receptor gamma, PRDM16, PR domain containing 16; RIP140, receptor interacting protein; SIRT1, sirtuin; SM, systems medicine; SNS, sympathetic nervous system; SUA, serum uric acid; TIF2 transcriptional mediator/intermediary factor 2; UCP1 uncoupling protein 1; VEG vascular endothelial growth factor (VEGF); VAT, visceral adipose tissue; WAT, white adipose tissue

Introduction

The global impact of obesity on health

Obesity is a recent problem in Western countries that has large economic, social and health implications. Between 2011 and 2014, roughly 36.5% of adults were estimated as overweight in the United States, with more than 40 % of these individuals being middle-aged.[1] This is especially problematic given that obesity can compound other health problems and chronic diseases that are becoming more pronounced in this age category. Importantly, the obesity problem is not likely to subside any time soon, as obesity rates have steadily risen since 1990, especially in children.[2,3] These observations also suggest that public health strategies aimed at preventing adiposity, in addition to treatment of the disease and its resulting complications, will have a significant impact on decreasing obesity, especially with regards to children and at-risk youth during early development. To start prevention at an early age, a thorough understanding of the factors and circumstances that lead to obesity is important. If nothing is done, as many as one billion adults might be obese by 2030.[4]

It is well established that obesity has a causative link to chronic conditions such as cardiovascular disease, diabetes, arthritis and chronic inflammatory diseases. However, the physiological and molecular mechanisms that underlie this link are not well understood. In order to truly educate the patients on the best dieting habits and lifestyle choices, it is important to understand the biochemical and biophysical mechanisms that drive the pathogenesis of obesity and the involved mediators.[1–14]

The development of obesity may not be the simple readout of the net caloric intake of an individual, as some patients are more prone to gain weight than others, even if they practice similar dieting strategies and lifestyle habits. Therefore, there may be additional factors present that mediate or mitigate the development of muscles and the storage of lipids in the body; these factors may differ from person to person

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[2]Ogden CL, Fakhouri TH, Carroll MD, et al. Prevalence of Obesity Among Adults, by Household Income and Education — United States, 2011–2014. *MMWR Morb Mortal Wkly Rep*. 2017; 66:1369–1373.

[3]de Onis M, Blossner M, Borghi E. Presentation at ONAND: Global prevalence and trends of overweight and obesity among preschool children. 2015.

[4]Kelly T, Yang W, Chen CS, et al. Global burden of obesity in 2005 and projections to 2030. *Int J Obes (Lond)*. 2008;32:1431–1437.

and thus factor into determining the outcome of weight reduction. The exploration of such factors is one of primary goals of the Pinewood Centre study.

The body stores fat in adipose tissue (AT). Therefore, to both understand the factors that underlie the development of obesity on a molecular, organic and systemic level and to develop possible treatment and health management strategies against obesity, one must also understand the architecture, molecular structure and biochemical and biophysical function of adipose tissue (AT). Since the early 2000's, the understanding of AT has shifted from being merely a location for fat storage to an entity behaving like a functional organ.[5] In this context, an area of special interest further explored in this study and medicine, in general, is metabolically active visceral fat, or white adipose tissue (WAT).[6]

Materials and methods

Assessing the role of wat in systems medicine

As adipose tissues receive and integrate a variety of signals from the organism that instruct the cells to store or mobilize lipids, the Pinewood Center Study focused on the influence of endocrine, neurological and immunological factors known as the neuroendoimmunologial (NEI) system in adipose tissue. The complex, integrated crosstalk that underlies the communication within this network is also referred to as Systems Medicine (SM). The aim of this STUDY was to establish a framework for a Dynamic Congruence Model that describes the NEI system and its impact on White Adipose Tissue (WAT) development and maintenance. The NEI system itself is supported by several other systems, namely the gastrointestinal, respiratory and circulatory systems. Furthermore, genetic information supplies the blueprint upon which these systems are built.

A truly systemic view of the organism as a whole should therefore also consider the role that these support systems play. Do they simply provide the infrastructure and guidelines by which the NEI interacts with WAT? Or is their role more dynamic in nature, shaping the interactions between the NEI system and WAT, or interacting themselves with the WAT? A truly systemic view should take these additional systems into consideration, even though the primary focus is on the NEI system. As an organ and part of a living systems model, adipose tissue is dynamic and responsive to internal and external stimuli; these stimuli elicit a molecular reaction that mediates changes in homeostasis and development. One example of an external stimulus is a hormone like insulin that interacts with receptors at the surface of adipocytes, activating intracellular enzymes that either aid in the mobilization of lipids as fatty acids or their storage as triglycerides.7 Understanding the contribution of the WAT organ complex to the overall physiology of the organism is an important goal in many clinical applications and practices, as it can aid the development of treatments and therapeutic interventions to facilitate weight reduction and reduce the risk for conditions such as Cardiovascular and Inflammatory Disease. Even the author himself takes a vested, personal interest in this area after having lost over 60 lbs. almost 12 years ago. This study investigates the hypothesis that the endocrine, immunological and autonomous nervous system are involved in the communication of WAT with the remaining organism.

The role of adipoines in homeostasis

Originally, adipose tissue (AT) was mainly perceived as a passive, physiologically inert storage place for fat, fuel for thermogenesis and/or as a protective layer against changes in the environmental temperature, mechanical impacts and friction from internal organs and bones. More recent findings indicate that AT is more dynamic in its functions, secreting a number of endocrine factors, such as sex steroids, glucocorticoids, and angiotensin, as well as the two classical adipokines leptin and adiponectin.[8,9]

Adipokines are peptides that act both locally in an autocrine/paracrine way and globally within the endocrine system. They regulate appetite, insulin sensitivity and glucose metabolism. They also regulate the rate of lipid assimilation, vascular function, blood coagulation, and immunity. Collectively, adipokines are produced by AT to regulate physiological homeostasis; dysregulation of adipokines is linked to hypertrophy and the transition from lean to obese AT.[10,11]

Homeostasis in AT is critical to its energy balance, and imbalances in the ratio of lymphocytes and monocytes/macrophages to adipocytes can result in metabolic disorders, diabetes or obesity.[12,13] AT is innervated by the sympathetic and parasympathetic nervous system;[14] via the hypothalamus, the autonomic nervous system mediates various functions in Adipose Tissue, such as the balance between lipolysis and adipogenesis as well as thermogenesis. Several of these processes involve the secretion of specific hormones or peptides, such as adipokines or neuropeptide Y.[15]

Adipose tissue does not only consist of mature adipocytes. Other types of cells associated with AT include immunocompetent cells such as monocytes/macrophages, T and B lymphocytes, mast cells, dendritic cells, neutrophils, eosinophils, and undifferentiated adipose precursor cells. AT produces a pro-inflammatory and anti-inflammatory hormone that greatly affect the metabolism including adipolin, visfatin, adipokines leptin, resistin, omentin, adiponectin and cytokines such as pigment epithelium-derived factor (PEDF), and progranulin (PGRN) tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6).[16,17,18,19] The proinflammatory hormones produced by AT may increase the likelihood of insulin resistance, obesity, and

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cardiovascular problems. The risk is decreased by anti-inflammatory and insulin-sensitizing adipokines such as adiponectin, adipolin, and omentin, as well as PEDF and PGRN.[20,21,22]

AT is present ubiquitously, often in the form of small fat deposits, secreting dozens of different hormones and cytokines. This qualifies it as the largest endocrine organ in the body. Adipokines also induce processes in the peripheral and the central nervous system, implicating AT in the processes that lead to peripheral diabetic neuropathy. TNF-α and macrophages associated with peripheral diabetic neuropathy are linked to with diabetic microvascular complications.

The dynamic integrated model of the Pinewood study research

While previous research has focused on the individual components of each of the systems mentioned in the Introduction as an organ system rather than an inert lipid storage, the underlying paradigm of this study is based on the novel idea that Dynamic Congruence emanates from the interconnection of neurology, immunology, and endocrinology to form a neuroimmunoendocrine (NEI) system in a Systems Medicine (SM) model. The intention was to derive Conclusions based on existing studies and consolidate them into a dynamic integrated model. This study intended to provide an understanding of homeostasis and provide a framework for the development of future study and clinical applications targeted at the current obesity epidemic.

The Pinewood study involved the measurement of 82 health-related factors, such as body fat percentage, serum glucose levels, activity of the autonomous nervous system etc. in 30 patients at the Pinewood Health Center in Toronto, Ontario. This sample was used to quantify various factors describing the subsystems involved in the cross talk of the NEI master systems. With regard to investigating this issue, adipose tissue is involved with the autonomic nervous system, the endocrine system and the immune system that all have influence over AT and *vice versa*. In addition, DNA, gastrointestinal, pulmonary and circulatory systems may play a role as well. Therefore, in the context of a living system and with all other systems being held constant, this study explored whether or not Dynamic Congruence be demonstrated through the following equation.

$$\sum QEME_{1-7} = f_1\left(E_e\right) + f_2\left(E_n\right) + f_3\left(E_i\right) + f_4\left(E_g\right) + f_5\left(E_c\right) + f_6\left(E_p\right) + f_7\left(E_{ge}\right)$$

Here, f_1 represents the endocrine system (E_e), f_2 the neurological system (E_n), f_3 the immune system (E_i), f_4 the gastrointestinal system (E_g), f_5 the circulatory system (E_c), f_6 the pulmonary system (E_p), and f_7 the genetic system (E_{ge}). This equation suggested that the organism is a congruent system that moves away from chaos and disorder.

It is important to note that the data measured in this study represent only the initial step in the development of a framework for dynamic congruence.The research was somewhat limited by the type of variables collected and the resolution provided by these variables. For example, measuring blood glucose concentration as a continuous quantitative variable, as done here, allows for better quantification that than just the information 'high' and 'low' as in questionnaire derived metrics. Another limitation of The Pinewood Study was the lower number of patients – a larger, stratified sample may allow for a more detailed analysis.

A question of dynamism and homeostasis

There are multiple systems that interact with each other to guarantee the functioning of a given organism. The major premise of this study is that the Neuroendoimmunological (NEI) system interacts with White Adipose Tissue (WAT) to establish and maintain homeostasis within the human organism, under additional consideration of the gastrointestinal, respiratory, circulatory and genetic systems. Even though one might regard those systems as passive support structures for the organism, their function may be more dynamic. For example, genetic information is not static but rather read out in a dynamic manner. While the endocrine system may mobilize cells to produce a certain hormone within a short time frame, for example, insulin after an increase in blood glucose concentration, changes to the gene expression profile are often implemented as long-term changes. If the body consistently needs to produce a certain hormone, increasing the transcription of the genes that synthesize that hormone may be a long-term solution. Furthermore, recent observations have shown that the circulatory, respiratory and gastrointestinal systems themselves are dynamic. For example, dependent on their own metabolic state, neural impulses can act on blood vessels to constrict or dilate them and thus regulate the amount of oxygen and nutrients that flows into the tissue[23] ; likewise, the permeability of the blood-brain barrier – and likely other blood-tissue barriers – is highly selective and can be regulated by a variety of factors, suggesting that communication between the vasculature and various tissues of the body is strongly regulated.[24,25] The molecular and cellular base of pulmonary function is less well understood; however, the respiratory system likely interacts with the circulatory and neurological system. For example, Community-Acquired Pneumonia (CAP) can often lead to cardiac arrhythmias and myocardial infarctions together with an upregulation of the sympathetic system.[26] And lastly, the gastrointestinal system offers a multitude of interactions, for example with the immunological or the neurological system.[27,28]

This article will focus on the interactions of these various physiological networks on White Adipose Tissue (WAT). Specifically, we will consider the following questions:

1. What are the modulators of homeostasis in the AT?
2. What specific growth factors, cytokines, and immune receptors are involved?
3. How does Adiponectin suppress metabolic functions?
4. With regards to the autonomous nervous system, while β_3 receptors are predominantly found in brown adipocytes and function in thermoregulation, what are the neuronal factors

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and neurochemicals that regulate white adipose tissue (WAT)? In this context, what function is governed by the hypothalamus around hunger, satiety, and temperature regulation?

5. How are blood flow and respiratory volume regulated to enable the interactions of the NEI system with AT? What is the role of the gut-brain axis in regulating the interactions of the autonomous nervous system with AT?
6. What cellular receptors, such as nuclear receptors, are involved and which signaling pathway are they part of?
7. What genetic influences are involved in the expression of these proteins and communicating molecules; what accounts for the variable degrees of body fat storage in different obese individuals?

Within the scientific community, one expects that the relevance of this topic is to demonstrate the complexity and the congruency of the NEI system. The resulting framework can serve as a model to understand other tissues that have not been fully characterized with respect to their metabolic activity profile.

In addition, the research may lead to the development of therapies based on the Dynamic Congruence model that are aimed at mitigating metabolic changes in a specific tissue or organ in order to treat chronic diseases or prevent their onset in the first place.

Finally, this article will discuss the clinical relevance that this data revealed and how it will lend itself to further study and investigation.

Current findings of the physiological role of white adipose tissue

As mentioned previously, adipose tissue is controlled by a multitude of central regulatory systems, most notably the neurological system, the endocrinological system and the immune system. The regulation is often complex and mutual. For example, any impulses that are sent via the nervous system to regulate AT composition through the thalamus or hypothalamus are modulated by hormones secreted by adipocytes that function in an autocrine or paracrine manner, such as Leptin.[29] At the same time, there may be some crosstalk from the AT back to the hypothalamus, as that area contains several Leptin Receptors, establishing a complex network based on feedback loops.[30] Likewise, recent studies suggest that obesity causes chronic inflammation, which is a condition that involves the immune system, as proinflammatory macrophages have been shown to accumulate in Visceral Adipose Tissue (VAT). Interestingly, adipocytes linked to obesity are displaying Natural Killer (NK) cell receptor NCR1 on their surface, and once NK cells localize within the adipocytes, they were seen to secrete interferons that induced the differentiation of pro-inflammatory macrophages and promoted insulin resistance.[31] These studies suggest that there is a crosstalk between the immune system and adipose tissue, as adipocytes can attract specific immune cells and engagement of immune cells can indeed influence the sensitivity of AT to hormones like insulin that are physiological regulators of metabolism. Adipose tissue itself secretes adipokines and other hormones that have a strong effect of glucose homeostasis and other functions and signify adipose tissue as an endocrine organ itself.[32]

The historical traditional view of adipose tissue

As discussed before, adipose tissue was originally seen as a mere passive store of fat and energy. However, researchers had soon discovered that there were different shades of fat tissue in the body – brown, beige and white.[33] While brown adipose tissue (BAT) was soon found to be involved in thermogenesis,[34] white adipose tissue (WAT) was still mainly regarded as passive storage of fat, with beige tissue forming a mix or intermediate between both tissues. The basic function of BAT is to maintain a stable body temperature in response to cold stress. Like adipose tissue in general, they store metabolic energy in the form of lipids and fatty acids and contain mitochondria to break down fats in a process called fatty acid oxidation. In contrast to the majority of other cells in the body, BAT cells have uncoupled the breakdown of fatty acids from the synthesis of ATP. The energy that is contained in fatty acids is therefore completely transformed into heat.[35] Importantly, brown adipose tissue can expand in reaction to sustained cold and dietary stress.[36]

The storage of fat in white adipose tissue does have an important physiological role – without WAT, lipids would accumulate in different tissues throughout the body and interfere with the metabolism in the cells in which they were stored, hampering normal physiological processes.[37] However, Flier, Friedman, Spiegelman, and others showed in the 1980s and 1990s that adipocytes were the source of a multitude of hormones and secretory factors, such as adipsin, adiponectin, leptin and other adipokines. In addition, adipose tissue also contained significant amounts of pro-inflammatory cytokines, suggesting a connection between adipose tissue and the immune system.[38]

Interestingly, at the same time that WAT was found to be endocrinologically active, researchers also found that it changed its appearance as a response to cold stress. Extracellular matrix was reduced and the number of gap junctions connecting the cells as well as the mitochondrial volume both increased. At the same time, the cells showed several metabolically active structures, resembling newly emerging adipocytes, while innervation and vascularization both increased. Thus, upon cold stress, WAT started to adopt several characteristics of BAT. These observations showed 'beige adipose tissue' as a third type of fat tissue; they also suggested that beige adipose tissue resembles a transitional state between BAT and WAT, and that those two tissues have the capacity to transform into one another.

The three types of fat tissue: white, brown, and beige

As mentioned above, the main function of brown adipose tissue (BAT) is to generate heat as a response to cold stimuli. To that extent,

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mitochondria in BAT cells are enriched with Uncoupling Protein 1 (UCP1), also called Thermogenin. In general, mitochondria generate energy by oxidizing NADH + H^+, building a proton gradient across the inner mitochondrial membrane. The energy from this gradient is then used to drive the synthesis of ATP from ADP + P_i. Thermogenin shortens this cycle by enabling the passage of protons back across the mitochondrial membrane. The energy that is freed in this process takes the form of heat, which contributes to thermogenesis. Thermogenin is activated in response to norepinephrine from sympathetic neurons, which then binds to the cells' β-adrenergic receptors.[39,40]

White adipose tissue (WAT) has a central role in converting glucose from the blood into fatty acids, which are stored as triglycerides – also known as fats. After the consumption of a meal, the blood glucose concentration increases, and insulin stimulates the uptake of glucose into adipocytes. The newly arrived glucose undergoes glycolysis, however, not to generate energy. Instead, glycerol-3-phosphate, a product of this process, is used to generate triglycerides together with fatty acids from the liver and the intestines. These triglycerides are stored in the form of lipid droplets within the cells, from which fatty acids can be released predicated upon the energy needs of the organism. In this paradigm, WAT is used as an energy storage device within the body.[41] Previously, however, WAT has been found to have a plethora of additional functions, involving nearly every other organ system within the body: appetite regulation, immunity, angiogenesis and control of vascular tone, fibrinolysis and coagulation, and even reproduction. It is not clear to which extent WAT functions as a systemic regulator of these processes or whether it regulates them on a more local level to facilitate its own functionality. However, it seems clear that white adipose tissue is indeed more than just an inert fat storage space. The molecular and biochemical base of these interactions is just beginning to be understood, and it will be very interesting to see how WAT interacts with other organ systems in the body.[42]

Beige adipose tissue appears to have an intermediate role between white and brown adipose tissue. As mentioned above, the application of cold stress to WAT induced structural changes in the tissue and the appearance of adipocytes that resembled brown adipocytes. In addition, the recruitment of blood vessels through the enhanced expression of Angiopoetin 2 and Vascular Endothelial Growth Factor (VEGF) in transgenic mice has been shown to be involved in the '*browning*' of white fat tissue, which essentially transforms WAT into beige adipose tissue. It is not clear whether beige adipose tissue is simply a mix of brown and white adipocytes, a transitional tissue between WAT and BAT, or a tissue with characteristics distinct from white and brown fat. Molecularly, beige fat carries markers of white and brown tissue as well as markers that seem to be unique for beige tissue; however, it is unclear whether it fulfills functions different from WAT and BAT.[43] More research into the function of WAT and BAT will likely also generate more findings about the function of beige adipose tissue.

The anatomy and histology of adipose tissues

Adipocytes in white, brown or beige tissue derive from mesenchymal precursors in paraxial tissues; fat tissue is thus mesodermal in origin and consequently often found close to muscle tissue.[44] It is also often found close to endothelial cells and neurons, which provide it with nutrients and neuroendocrinological signals, respectively. In fact, angiogenesis plays an important role in the expansion of BAT and the transformation of WAT into beige adipose tissue, but also in the expansion of WAT. Increasing WAT abundance without proper angiogenesis and the resulting hypoxia have been linked to WAT dysfunction in obese[10] patients.[45,46]

There are several characteristic locations for white, beige and brown adipose tissue in the human body [1]. While WAT is predominantly found in subcutaneous locations – i.e. underneath the skin (scWAT), BAT can be found at other distinct places: in deep layers of neck fat; beneath the clavicular bone as so-called supraclavicular BAT (supBAT); close to the adrenal gland as periadrenal BAT; and intermingled in scWAT, based on the expression of specific genetic markers. Beige fat tissue can be found in supraclavicular, periadrenal and subcutaneous locations mixed with other fat types. However, it can also be found as a separate unit, for example, in intermediate layers of neck fat. Even those different deposits outlined above for WAT, BAT, and beige tissue can be subdivided into further, even smaller subcategories. Importantly, all of these deposits can be distinguished by individual signatures of differentially expressed genetic markers. The functional or anatomical relevance of these markers is not clear; at the very least, the observation that these signatures are distinct supports the hypothesis that adipose tissue is not just some passive energy storage device.[47]

Histologically, WAT is dominated by large lipid droplets, lipid-containing vacuoles that fill almost the complete cell, leaving a thin layer of cytoplasm with flattened nuclei.[48] WAT cells can be quite large and measure up to 0.2 mm in diameter. Because they only contain a single vacuole filled with lipids and derivative products, they are also called *unilocular*. WAT is sparsely vascularized, although each adipocyte is in contact with at least one blood vessel.[49] BAT, in contrast, consists of '*multilocular*' cells with several smaller fat droplets and an abundance of mitochondria that are positive for UDP1/Thermogenin. Brown adipocytes grow up to 0.06 mm in diameter, and BAT tissue contains significantly more blood vessels than WAT tissue. The rich vascularization and the abundance of mitochondria gives the tissue a '*brown*' color.[50,51] Beige adipose tissue has both features of white and brown adipose tissue.[52]

Brown, beige, and white adipose tissue have their origins in mesenchymal precursors from the mesoderm. These precursors can either be positive or negative for the transcription factor MYF5. $MYF5^+$ mesenchymal precursors give rise to both BAT and WAT

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[48]Campioli E, Carnevale G, Avallone R, et al. Morphological and receptorial changes in the epididymal adipose tissue of rats subjected to a stressful stimulus. *Obesity*. 2011;19(4):703–708.
[49]Albright AL, Stern JS. Adipose tissue. In: *Encyclopedia of Sports Medicine and Science*. In: TD Fahey, editor. 1998.
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[51]Charmaine S Tam, Virgile Lecoultre, Eric Ravussin. Brown adipose tissue: mechanisms and potential therapeutic targets. *Circulation*. 2012;125(22):2782–2791.
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adipocyte precursors, while MYF5$^-$ cells only develop into WAT adipocyte precursors. Thus, in the end, differentiated BAT cells have their lineage originate exclusively in MYF5$^+$ cells, while differentiated WAT cells can be derived from both MYF5$^+$ and MYF5$^-$ cells. The fact that both MYF5+ and MYF5- precursors can end up contributing to WAT cells is in line with the observation that WAT cells can transform into Beige Adipose Tissue (BeAT). Cells of the latter tissue can be characterized by their expression of UCP1, which is also one of the most significant expression markers that distinguish BAT from WAT.[53] In addition, endothelial precursors can contribute to both WAT/BeAT and BAT, while BAT can derive some of their cells from muscle satellite cells as well.[54]

Recent experiments with rodents have shown that three different molecular signaling processes contribute to the differentiation of BAT, BeAT and WAT adipocytes. Inducing Peroxisome Proliferator-Activated Receptor Gamma (PPAR-γ) dependent cascades in BAT precursors enhances their differentiation into BAT cells, while treating WAT precursors with PPAR-γ agonists leads to the development of beige adipocytes, suggesting that WAT cells can indeed differentiate into BeAT cells.[55,56,57] Other transcription factors, such as Receptor-Interacting Protein 140 (RIP140) and Transcriptional mediator/ Intermediary Factor 2 (TIF2), aid in implementing WAT cell fate and differentiation.[58] Interestingly, the expression of Uncoupling Protein 1 (UCP1) and other thermogenins is not necessary for induction of BAT cell fate: deleting the transcription factor PR Domain Containing 16 (PRDM16) in adipose tissue only inhibits the expression of thermogenic genes, yet the cells still develop cellular features characteristic of BAT cells.[59]

A second level of control in the development and transition of WAT, BeAT, and BAT are epigenetic mechanisms, such as Sirtuin (SIRT1) mediated deacetylation of PPAR-γ. The latter promotes BeAT cell development in WAT, and SIRT1-mediated deacetylation of MyoD has been proposed as a repressor of myogenic differentiation of BAT adipocytes.[20,21]

A third level consists of micro-RNA (*mi*RNA). miR-155 interacts with *CCAAT Enhancer Binding Protein Beta* (C/EBP-β) in BAT adipocytes and determines whether the cells should proliferate or differentiate and thus likely controls BAT growth. Furthermore, miR-27 inhibits brown and beige adipocyte differentiation, while miR-196a enhances these processes. Cold exposure blocks miR-27 and increases miR-196a expression, suggesting that environmental influences determine the specific fate of adipose tissue.[60,61]

How the neurological system crosstalks with adipose tissue

Anatomically, White Adipose Tissue (WAT) is connected to the brain via both the sympathetic and parasympathetic nervous system, as neurons of both compartments of the autonomous nervous system can be retrograde labelled using pseudorabies virus strains, injected into WAT.[62] The sympathetic nervous system (SNS) is thought to mediate responses to a shortage of energy, for example during fasting or exposure to low temperatures. The cold response requires that all three adipose tissue types – brown, beige and white – are coordinated to mediate thermogenesis by Brown Adipose Tissue (BAT). Lipid stores inherent within the cells of the WAT are opened, releasing triglycerides, and lipolysis is induced within BAT cells. This provides fatty acids that both stimulate the thermogenic *Uncoupling Protein 1* (UCP1) and serve as '*fuel*' generating thermogenic energy in the process. In addition, sustained SNS activation promotes the expression of thermogenic genes, ensuring long-term regulation of thermogenesis.[63] The role of Beige Adipocyte Tissue (BeAT) is less clear in this process, however, genetic ablation of BeAT leads to obesity upon the decreased function of BAT in thermogenesis, suggesting that this tissue does play a role in the overall regulation of adipose tissue function.[64] It should be noted that cold exposure also stimulates angiogenesis in WAT due to an upregulation of Angiopoetin 2.[65] Furthermore, angiogenesis has been found to play an important role in the expansion of WAT due to increased energetic needs; conversely, WAT hypertrophy without adequate vascularization leads to hypoxia and possibly WAT dysfunction in obesity. However, whether angiogenesis is required for a functioning adipose tissue is unclear, as both promotion or genetic ablation of adipose tissue angiogenesis can improve the metabolic function of AT; it may be that hypoxic adipocytes are eliminated via apoptosis, leaving a smaller number of adipocytes that show normal metabolic function. In any case, the vasculature seems to be linked to a functioning WAT.[66]

Despite its anatomical connection, the functional impact of parasympathetic innervation on the WAT appears to be less significant.[67] Earlier studies found that after ablation of the vagal nucleus, which is connected to WAT via the parasympathetic nervous system (PSNS), the insulin-mediated uptake of glucose and free fatty acids is significantly reduced, while the activity of Hormone-

[53]Peirce V, Carobbio S, Vidal-Puig A.

[54]Peirce V, Carobbio S, Vidal-Puig A.

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[63]Mazidi M, Katsiki N, Mikhailidis DP, et al. The link between insulin resistance parameters and serum uric acid is mediated by adiposity. *Atherosclerosis*. 2017;270:180–186.

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[66]Mazidi M. *'et al'*..

[67]Tano, J. Y., Schleifenbaum, J., & Gollasch, M. (2014). Perivascular Adipose Tissue, Potassium Channels, and Vascular Dysfunction Significance. Arteriosclerosis, thrombosis, and vascular biology,34(9), 1827-1830. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/25012133

Sensitive Lipase (HSL) is significantly increased.[68] However, several characteristic aspects of PSNS innervation, such as parasympathetic ganglia located close to WAT deposits or typical biochemical and neurochemical markers are not found near WAT fat deposits.[69,70] In addition, when additional studies were performed that used drugs to block sympathetic innervation, pseudorabies virus labelling was not observed anymore. Unfortunately, no genetic ablation has been performed to elucidate whether parasympathetic innervation is required for WAT function. The surgical and drug-based techniques that have been used so far to elucidate the PSNS impact on WAT are much less specific than genetic techniques. However, there is a wealth of studies that establish a functional link of SNS and WAT. Thus, even though SNS and PSNS are usually correlated with each other in an agonistic vs. antagonistic way, adipose tissue may be an exception to this rule, in that only the SNS, but not PSNS, has a functional impact on WAT homeostasis. However, there still is the possibility that PSNS innervation of WAT is mediated by an as yet unknown mechanism.[71]

Measuring body-mass-index, body fat and basal metabolic rate

Body-mass-Index (BMI), Body Fat and Basal Metabolic Rate (BMR) are parameters that present basic measurements for metabolic parameters in the human body. The BMI is calculated as the mass of the body in kilograms, divided by the square of its height in meters. The basic of the BMI is to estimate whether someone is obese, overweight, normal weight or underweight by quantifying their weight compared to their height. The larger the latter factor, the heavier someone will be, even at a normal weight. Based on empirical findings, the assumption is that the weight of a person of a specific body composition – underweight/normal/overweight/obese - increases with the square of its height. That means that someone with the same body composition who is twice as large will not weigh twice as much, but *four* times more. This rule of thumb holds remarkably well in normal weight and height ranges.

However, the overall weight can be misleading when determining if someone is normal, under or overweight. Our bodies are not one homogenous mass. They consist of bone and cartilage, nerve cells, muscle, and fat. All of these tissues have different densities. Two people of the same height and total body volume will have different BMIs, if one of them has very little fat and a lot of muscle and the other one a lot of fat and very little muscle. In fact, the muscular guy may even show a BMI that falls into the overweight or obese category, while the other one is 'healthy'. Such a result would obviously be misleading. In another example, a competitive bodybuilder will show a high weight because of the enhanced muscle mass, but that does not mean he is obese, even if the BMI is high.

Therefore, another measurement – the body fat percentage – is used to determine the body composition in regard to fat and muscle content. A general rule of thumb is that fat starts to visibly recede, and facial features become visible when the body fat percentage falls below 20%.

As a third metabolic parameter, one can measure the *Basal Metabolic Rate* (BMR). This rate measures the minimal energy expenditure needed to keep metabolism running at rest. The BMR is measured in calories per time unit; for practical purposes, it can be displayed as calories needed per day. If the daily number of calories taken in through nutrition exceeds the BMR, the individual may become overweight or obese, as the extra energy becomes stored in the form of WAT. Therefore, the BMR is one of the parameters that may have an influence on the increase or decrease of WAT.

Measuring the body-mass-index

Measuring the BMI is relatively simple. As mentioned above, one takes somebody's weight in kg and divides it by the square of his height in m. The more overweight someone is, the higher his BMI, the more strongly will his weight increase with height, as the *square* of the height contributes to the weight:

$$\text{Weight [kg]} = \text{BMI} \cdot \text{height}^2 \text{ [m}^2\text{]}$$

For example, a Body-Mass-Index of BMI = 20 indicates normal weight. Someone who is 1.80 m large (5 ft 11 in) can be expected to weigh 64.8 kg (142.5 lbs.) if he is normal weight. If he is obese, however, with a Body-Mass-Index of BMI = 40, he can be expected to weigh twice as much: 129.6 kg (285 lbs.). The BMI is different for men and women of different ages. Generally accepted estimates are that a BMI < 18.5 is underweight, 18.5 – 25 normal, 25 – 30 overweight and BMI > 30 is regarded as obese.[25]

Measuring body fat, fat-free mass, and BMR

The body fat (BF%) is simply the percentage of the total body mass that is fat – more specifically, adipose tissue. There are several methods to measure it; the most common is the bioimpedance analysis, which measures the ability of the body to conduct a small electrical current. As fat contains less water than other tissues in the body, it will conduct electricity less efficiently and therefore one can use this ability to estimate the percentage of the body that consists of fat.

Bioimpedance measurements are built in many modern balances to measure body weight or in handheld devices, where the user is grabbing a metal plate through which a low current is sent. For more accurate measurements, electrodes are used and attached to the body. The measured resistance can then be used to calculate the body-fat percentage, using formulas, graphics or tables. The fat-free mass (FFM) is simply the non-body-fat percentage of the total weight:

$$\text{FFM} = (1 - \text{BF\%}) \cdot \text{weight}.$$

For example, if someone weighs 75 kg and has a body fat percentage of 20%, the FFM would be:

$$\text{FFM} = (1 - 0.2) \cdot 75 \text{ kg} = 0.8 \cdot 75 \text{ kg} = 60 \text{ kg}.$$

Accordingly, the individual in this example has 15 kg of adipose tissue in his body.

The Basic Metabolic Rate (BMR) is usually not measured but estimated using the empirical *Harris-Benedict formula*. In its most recent form, this formula uses a basic number; adds ten times the body weight in kg; adds 6.25 times the height in cm; and subtracts five times the age in years.[27] The formula is valid for both men and women; the basic number is just different.

Men: BMR = 5 + 10 · weight [in kg] + 6.25 · height [in cm] – 5 · age [in years].

Women: BMR = - 161 + 10 · weight [in kg] + 6.25 · height [in cm] – 5 · age [in years].

Women have a lower BMR than men of the same weight, height and age, and the BMR depends on all other factors in the same way.

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[69]Tano JY, Schleifenbaum J, Gollasch M.

[70]Giordano A, Song CK, Bowers RR, et al. White adipose tissue lacks significant vagal innervation and immunohistochemical evidence of parasympathetic innervation. *Am J Physiol Regul Integr Comp Physiol.* 2006;291: R1243–1255.

[71]Giordano A, *'et al.'*

For example, a 75 kg man, 180 cm tall and 35 years old would have a BMR of

$$BMR = 5 + 10 \cdot 75 + 6.25 \cdot 180 - 5 \cdot 35 = 1{,}700.$$

For women, the BMR would be BMR = 1,534.

Beyond using the BMR in this study, one can multiply the BMR with a factor between 1.2 and 1.9 and determine our daily calorie needs depending on our activity.

Additional methods and materials

Healthy lifestyle and personal control questionnaire

Patients were asked to self-assess with regards to their dietary health choices, dietary harm avoidance habits, daily routine, organized physical exercise, and social and mental balance.[72]

Assessing adipose tissue with blood tests

There are numerous parameters that can be measured through blood tests that give us direct and indirect information about the status of adipose tissue within the body. Blood was taken in a Dynacare laboratory facility near the Toronto Pinewood Health Center in Ontario, Canada, through venipuncture, in accordance with Federal and local health requirements.

Lipid profiles

The amount of triglycerides and cholesterol can give us direct information about fat content in your body. These two substances are transported in the blood in the form of High-Density Lipoprotein (HDL) and Low-Density Lipoprotein (LDL) particles. Interestingly, under cold exposure, BAT is triggered to utilize lipids and fatty acids from WAT. These substances are transported in the form of HDL and LDL particles.[73] Therefore, measuring the lipid and cholesterol content in blood may be a suitable parameter of lipid homeostasis in the body.

Kidney profiles

Within the blood work panels, testing for sodium, potassium, creatinine and uric acid can give information about kidney health and function. However, several of those parameters have been linked to obesity, insulin resistance, and glucose homeostasis and may thus be useful as biomarkers for WAT function.

In an analysis of serum uric acid (SUA) levels among over 16,000 U.S. adults, there was a significant negative correlation between SUA levels and glucose/insulin homeostasis parameters.[74] Furthermore, high sodium intake has been correlated with adiposity. Specifically, a recent study has found that dietary sodium showed a statistical association with body weight, BMI, percent body fat, and subcutaneous abdominal adipose tissue mass, among others; interestingly, visceral fat does not seem to be impacted by sodium intake.[75] For potassium and creatinine, no direct connection to adipose tissue function seems to exist, although perivascular adipose tissue secret factors that regulate potassium channels within the smooth muscle cells that constrict the arteries adjacent to the adipose tissue.[76]

Heart rate parameters and autonomic nervous system

Heart rate variability was measured with the *Nerve Express* method. Briefly, various parameters are measured in an orthotest, where measurements are taken once in the supine and once in the upright patient position; during a Valsalva maneuver; and via long-term monitoring of a patient in real time. In addition, the physical fitness, wellness, and functional capacity are measured via the Health Express test (see Appendix for a more detailed description of the test preparation).

Mathematical modeling of dynamic congruence

The Pinewood Study served to establish a framework for the role of WAT in mediating various biological processes, the biological markers measured in this study are not particularly useful on their own, unless used to develop an experimental animal or cell culture model system. Rather, one can use the marker concentration to develop a model of Dynamic Congruence. With the measured parameters, the model can then be used to predict which of the parameters has the largest influence on Dynamic Congruence and thus explore significant avenues into potential therapeutic targets.

The dynamic congruence model (physio dynamic system)

Figure 1 shows a graphical representation of our body as a dynamic system and the proposed role of WAT as a subset within that system. In the model, several parameters of various systems, with appropriate correction and correlation factors, add up to provide a description of dynamic congruence. If an organism is in a state of dynamic congruence, one expects that changing one parameter will influence another parameter to change in the opposite direction, so that the equilibrium is restored. Mathematically, this means that the system will revert back to the original number. As the spring-like structures in Figure 1 and the qualifier 'dynamic' suggest, it may take the system a while before it '*swings back*' into the original state.

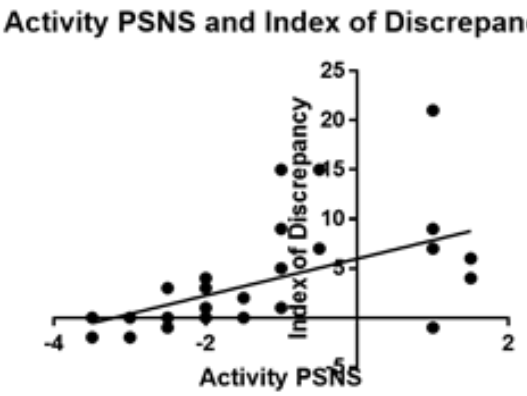

Figure 1 PSNS index of discrepancy.

Multiple regression analysis of the markers

Figure 1 also shows a multitude of connections. In theory, if all ten vertices in the model can interact with one another, one would be looking at the analysis of $\frac{1}{2} \cdot n \cdot (n-1) = 45$ different interactions. However, it is not clear whether all of these interactions have the same effect on each other; some of them may be independent of one another, others may have predictive value. For example, changing metabolic parameters after a large glucose intake may also affect the autonomous nervous system or the immune system. However, even if – in this example – the serum glucose concentration correlated with factors from the immune system, it is not clear whether there is a direct connection, or whether the immune system factors correlate with the autonomous nervous system, which then correlated with glucose concentration. Therefore, a multiple regression analysis will be used to define the factors that correlate with each other *if all other*

[72]Darviri, C '*et al*.'
[73]Heeren J, Scheja, L.
[74]Mazidi M,'*et al*'.
[75]Zhu H, ,'*et al*'.
[76]Tano JY, Schleifenbaum J, Gollasch M.

factors are kept constant. To keep the model simple, the regression analysis will be based on linear correlations. In theory, it may be possible that factors correlate non-linearly, yet this would add another level of complexity; it is easier to establish linear connection and then further refine the type of correlation in a follow-up study.

If one sets dynamic congruence and thus the equation to zero, one can solve the equation for one factor, for example, the sodium content in the blood. If one keeps all other factors constant at the value they had before, one can see how big the change percentage of the factor in question (here: sodium) is. The factor that yields the smallest percentage change must then be the one the system is most sensitive towards.

From all of this we can establish that there are several types of adipose tissue in the body – white, brown and beige. These tissues share common progenitors and can transform into one another to a limited extent. According to the Dynamic Congruence model, we can also conclude that a change in one parameter will yield an opposite change in another parameter. There are several biological markers one can use to describe the system and use a multiple linear regression analysis to determine which of the multiple factors that contribute to homeostasis has the biggest impact.

Results: the results of the pinewood study

The results of the Pinewood Study produced several regression equations, choosing to only include those independent variables that show a significant correlation ($p < 0.05$) with the dependent variable.

Body Cell Mass % = 47.97 – 0.78 · Body Fat %

Body Fat % = 38.75 – 0.81 · Body Cell Mass %

Glucose Serum Fasting = 1.83 ·Hemoglobin A1c – 0.07 · E.S.R. + 0.15 · CRP

Hemoglobin A1c = 2.12 + 0.46 · Glucose Serum Fasting – 0.06 · CRP

E.S.R. = -3.55 · Glucose Serum Fasting + 1.49 · CRP

CRP = 0.35 · E.S.R. – 3.20 · Hemoglobin A1c + 1.97 · Glucose Serum Fasting

There was no independent variable that significantly predicted the activity PSNS, activity SNS or the levels of TSH, suggesting that despite several significant correlations, there was no independent variable that would predict the value of any of these three factors if all other variables were held constant. On the other hand, Body Cell Mass percentage and Body Fat percentage only correlated with each other, all other factors held constant.

However, there was significant correlation between Glucose Serum fasting levels and Hemoglobin A1c levels – two metabolic markers, of endocrine influence - on one side and Erythrocyte Sedimentation Rate (E.S.R.) and C-Reactive Protein (CRP) – two inflammation markers - on the other side. This suggests that the data available here mostly show a relationship between metabolism and immune system. If one sets the equations on one side to zero, one could construct several equations that describe dynamic congruence. Those equations all show significant relationships between variables. If one sums the last four equations up, the following is derived (with Glucose Serum Fasting = GSF):

GSF – 1.83A1c + 0.07 ESR – 0.15 CRP = 0

- 0.46 GSF + A1c + 0.06 CRP = 2.12

3.55 GSF + ESR – 1.49 CRP = 0

-1.97 GSF + 3.20 A1c – 0.35 ESR + CRP = 0

The resulting equation is

2.12 GSF + 2.37 A1c + 0.72 ESR – 0.50 CRP = 2.12

This means that Glucose serum levels after fasting, Hemoglobin A1c and Erythrocyte Sedimentation Rate contribute positively to the dynamic congruence, while C-Reactive Protein levels contribute negatively. This postulate of course, would require further testing and validation.

One can use these factors to derive a dynamic congruence model according to the formula

$$\sum QEME_{1-7} = f_1(E_e) + f_2(E_n) + f_3(E_i) + f_4(E_g) + f_5(E_c) + f_6(E_p) + f_7(E_{ge})$$

as mentioned in chapter 1.4 above. The factors $f_1(E_e)$, $f_2(E_n)$, $f_3(E_i)$ etc. are derivatives from the multiple subsystems of the body, while the summation term on the left suggests dynamic congruence. There are two possibilities for how to approach this equation. If one assumes the dynamic congruence term is constant – that overall, the body will always keep one term constant or within a very defined range, then the factors f_i must all be correlated with each other. If f_1 doubles, for example, f_2 to f_7 will have to become reduced accordingly so the overall sum remains the same. Applied to the case studied here, the dynamic congruence formula could look similar to this:

$$\sum QEME_{1-7} = 2.12(GSF) + 2.37(A1c) + 0.72(ESR) - 0.50(CRP) = 2.12$$

These numbers are only a starting value and should probably be refined with more research data and/or further parameters.

In a second approach, one assumes the left term of the equation not to be constant. If, for example, the patient contracts a fever, the body temperature will go up and the body will be out of homeostasis. Under that assumption, one can integrate the terms for the autonomous nervous system, immune and endocrine as a representation of NEI:

$$\sum QEME_{1-7} = 2.12(GSF) + 2.37(A1c) + 0.72(ESR) - 0.50(CRP) + f_1(PSNS, SNS, TSH) + f(BCM, Body\ Fat) = 2.12$$

In any case, it probably makes sense to test patients with physiological stress tests and address whether several factors will change to keep homeostasis constant, or whether homeostasis assumes changing values.

Conclusions and future outlook

The results shown above suggest that different systems contribute differently to the overall homeostasis of the body. For example, none of the three parameters of the autonomous nervous system – activities of the parasympathetic and sympathetic nervous system as well as TSH levels – have any significant power to predict other variables, as judged by multiple regression analysis. Furthermore, metabolic parameters like body cell mass percentage and body fat percentage only have predictive power onto each other and no other variable. However, other metabolic parameters, like Hemoglobin A1c levels and glucose serum levels after fasting do predict parameters of the immune system, such as levels of C-Reactive Protein and Erythrocyte Sedimentation Rate.

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One caveat of these observations is that the chosen parameters do not represent the underlying system very well. It is possible to test different parameters and analyze their behavior under a statistical analysis, such as multiple regression analysis. Another caveat could be that all of the analysis in this study was done under the assumption that the parameters would all behave in a linear fashion. More advanced statistical technologies that use non-linear correlation may be necessary to fully capture the way in which parameters work together.

The statistical data used in this study show but a small window into the different parameters that can be measured in the human body. To completely correlate the different biosystems in the body in one formula, one could find the most relevant parameter for each system, potentially via multiple regression analysis within each system; for example, if eight parameters are describing the gastrointestinal system, one could do eight different multiple regression analysis with each parameter as the dependent variable. The variable that most often appears as being significantly correlated to all other variables could be chosen as the most significant descriptor of the system. Then, the descriptors of all systems could be combined into an equation that describes the body's homeostasis using the Dr. G.P. Einstein Sigma Quanta Physio Dynamic Systems model.

In any case, the G.P Einstein Model, as seen in Figure 3, can nicely point out how parameters correlate and describe the body's homeostasis, in the master systems and the subset organs, such as the WAT. It would be interesting to test some of the correlations experimentally using either physiological tests with volunteering participants, or animal models. These tests would have the advantage of directly determining which parameters are correlated on a cause-effect base. When using model organisms, one could even measure additional biological markers, such as DNA and protein levels, the morphology and histology of different organs etc.

As demonstrated in Figure 2, expansion of the model could also include an interventional model, postulated to have the input of Quanta Energy into the system as a potential therapeutic target, in the homeostatic model one could potentially predict clinical outcome. The limitation of cross sectional study such as the one conducted in this study is the establishment of only correlation and not causation and/or treatment. Further studies and different study design may also need to focus on whether the equation maintains a fixed value constant or is a changing value based on the health of the organism.

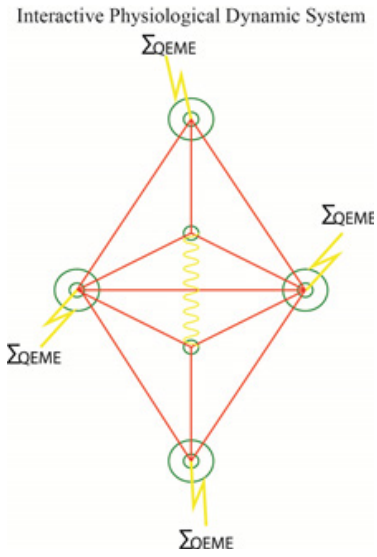

Figure 2 Therapeutic interventional model of dynamic physiological system.

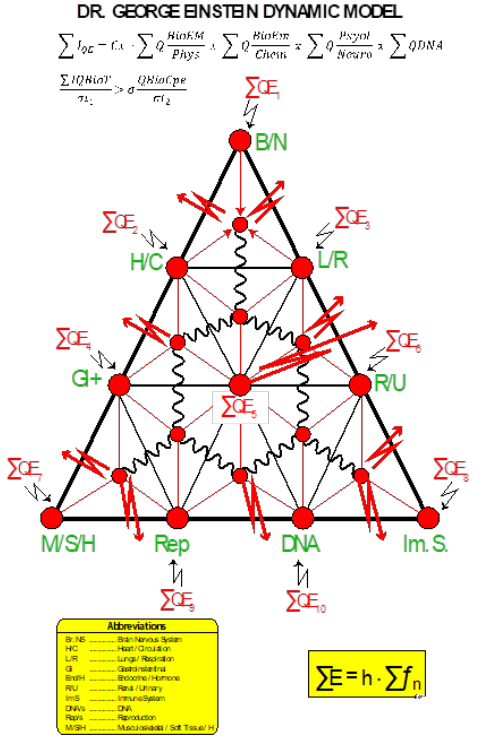

Figure 3 *Dr. George Einstein dynamic model.*

There is another possible future direction. In general, the observation that two variables are not significantly correlating within a multiple regression does not mean that there is no biologically relevant connection. Rather, it only means there is not enough evidence to reject the null hypothesis that states there is no correlation between the variables. There could always be other variables that do show a good correlation and predictive power in a multiple linear correlation. The important question is whether the chosen variables are representative of the biological subsystem they describe in the body. A possible extension of the study conducted here is to take all parameters that describe a specific subsystem – for example, the metabolism – and conduct multiple linear regressions to find the variable that correlated with most other variables. One could then make the assumption that a variable that shows the most statistically significant correlation to others may have the strongest predictive value in the subsystem it describes.

Subsequently, one can find those highly significant variables for each subsystem in the body and then do a multiple regression with all those variables to arrive at a form of the Dynamic Congruence equation, similar to the calculations shown above - with a smaller number of parameters.

Importantly, a significant correlation between factors in a multiple linear regression only makes a statement about the two or more variables changing significantly together. However, even if a correlation is significant, and a regression line can be derived, it does not mean that both variables are 100% dependent. It could be that 75% of the behavior of the dependent variable can be explained by the behavior of the independent variable while leaving 25% still to chance. This means that even if one adds the factors that correlate with each other for the Dynamic Congruence equation, there could still be an independent part within that equation; a part of dynamic congruence that moves independently of all factors in the equation. In biological terms, this would suggest that the body always tries to keep the overall balance, but that there are certain influences outside of its

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control. Deeper quantitative analyses have to be done to distinguish between a complete correlation, complete independence or partial independence of factors contributing to Dynamic Congruence. The analysis done in this study was merely a first, limited step into establishing the paradigm of Dynamic Congruence. Follow-up studies will likely be able to shed more quantitative light on the statistical behavior of the variables.

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Conflicts of interest

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