

THE THERMODYNAMICS OF METABOLISM, CARDIOVASCULAR PERFORMANCE AND EXERCISE, IN HEALTH AND DIABETES: THE OBJECTIVE OF CLINICAL MARKERS

C.S. KÖNIG, Research Fellow in Bioengineering, PhD, S. RAMACHANDRAN, Consultant Biochemist, PhD, J. GONZÁLES-ALONSO, Professor for Exercise and Cardiovascular Physiology, PhD, M.A. ATHERTON, Reader in Mechanical Engineering, PhD, M.W. COLLINS, Visiting Professor, DSc

From Brunel University, London, UK; and Postgraduate School of Pathology, Heart of England Foundation Trust, NHS West Midlands, UK

Correspondence to Prof. Michael Collins, School of Engineering and Design, Brunel University, London, UB8 3PH, UK. Tel: +44 1895 265405; Fax: +44 1895 256392; e-mail: collinmw@hotmail.com

ABSTRACT

Extensive experience in UK National Health Service metabolic syndrome/type 2 diabetes clinics highlights the need for convenient clinical marker(s) which can be readily used to indicate the success or otherwise of alternative therapies. In this paper we study the metabolic context of the healthy and diseased states, which points to the haemodynamics being a possible key in identifying candidate markers.

Human metabolism relates to two elemental thermodynamic systems, the individual cell and the human body in its entirety. The fundamental laws of thermodynamics apply to humans, animals, and their individual cells for both healthy and diseased conditions, as they are to classic heat engines. In compliance with the second law enhanced levels of heat are generated under exercise, heat itself being another factor modulating the cardiovascular response to physical exercise.

Nutrients and oxygen uptake occurs via the digestive system and lungs, respectively, leading to ATP production by the established metabolic pathways: this is controlled by insulin. These are then delivered to the cells via the haemodynamic system to satisfy local metabolic need. The supply and demand of oxygen are finely regulated, in part, via oxygen-dependent release of ATP from the circulating erythrocytes. Energy supply and demand are regulated to sustain muscle activity resulting in the body's output of measurable thermodynamic work—i.e. exercise. Recently a dynamic pathway model allowing quantification of ATP release from the erythrocytes and its contribution to oxygen supply regulation has been published.

However, metabolic uptake is well known to be greatly affected by disease such as the highly prevalent diabetes type 2 with insulin resistance and beta cell dysfunction having mechanistic roles. In 2010, over 25% of residents above 65 in the USA had diabetes 2. The complexity of the metabolic pathways means that monitoring of patient-specific treatment would be beneficial from a diabetic marker which may be haemodynamic-related and traceable via the local fluid dynamics.

Key Words: Thermodynamics; metabolism; cardiovascular performance; exercise; heat; glucose; ATP; insulin; type 2 diabetes

Thermodynamics and biology

While the Laws of Thermodynamics were formulated in the 19th century in the context of industrial revolution heat engines, it was realised from the start that they applied to the natural world as well. Today it is universally accepted that they are among the most fundamental laws of nature and, as presented in this paper, can give an underlying explanation of human metabolism and activity.

An outline of the fundamental concepts comprises the following. First is the extremely flexible concept of the system, of which there are three classes: isolated, closed and open. At the top is the isolated system of the universe, and of more interest, as containing the ultimate source of our energy, the almost isolated solar system. Biological assemblies, whether ecosystems, individual organisms or cells, are all open systems in the thermodynamic sense.

Second, are the key concepts of energy (a system property), heat and work (transfers of energy across the boundary) and entropy (the level of disorder). In simple terms for closed systems: energy cannot be either created or destroyed (1st Law) but that when energy is converted to a different form there is an inevitable waste of energy (2nd law) in the form of heat (with a rise in entropy). A very important concept is free energy, that part of energy which can be wholly usefully used. The terms energy, free energy and entropy result correspondingly from the pioneering thermodynamicists Lord Kelvin (British), Willard Gibbs (American) and Rudolf Clausius (German). It was Clausius who made the iconic statements ([1], p 168):

“The energy of the universe is constant. The entropy of the universe tends to a maximum.”

***Homo sapiens*: a thermodynamic system and its metabolism**

Human metabolism relates to two key thermodynamic systems; the *individual Homo sapiens* and a *single cell*. Because of the generality of the laws of thermodynamics, a human being has many characteristics of an engineering heat engine, e.g. an internal combustion engine. Essentially combustion in the latter-- with fuels burned in oxygen and emitting primarily carbon dioxide —is equivalent in the former to food consumption coupled with oxygen intake and carbon dioxide release. The names give it away—hydrocarbons and carbohydrates, respectively.

This has been examined in some detail in [1], as:

- i] thermodynamic input, energy in nutrition (food and drink)
- ii] thermodynamic outputs, internal energy consumption (like an idling car), plus external measurable useful work (exercise), plus generation of information/complexity (see Section 6. Brunelleschi, the complexity engine in [2], p. 188)
- iii] heat rejection to the environment.

This means that the essential thermodynamic metabolic indicator is the energy balance, confirming the standard approach of calorie considerations. Another confirmation is that once a system and its 3-D

boundary are defined, thermodynamics is not concerned with the system contents *per se* but focuses on the energy transfers. So here the outer skin forms a convenient boundary, thus permitting the straightforward reasoning above.

The human cell: a thermodynamic system and its metabolism

In engineering terms the human body is extraordinarily complex considering an adult human is made up of the order of one hundred trillion (10^{14}) cells. Despite this, the fundamental chemical thermodynamic processes are achieved within each cell itself. At the other extreme nutrition connects thermodynamically with the solar system. These cellular pathways have been summarised by Mikielwicz *et al* [3] as a series of chemical Black Box diagrams. Their especial focus is the food glucose and the body's energy-storage compound ATP.

The haemodynamic system; connecting organism and cell and regulating muscle activity

The body takes in nutrients and oxygen via the digestive system and lungs, respectively. At the micro-scale these are delivered by the flowing blood to the cells in accordance to the local metabolic need. The matching of oxygen supply and demand is finely regulated in part via an oxygen-dependent release of ATP from the circulating erythrocytes. Also, again at the micro-scale, the regulation of energy supply and demand is required to sustain muscle activity [4], [5] resulting in the body's output of measurable thermodynamic work—i.e. exercise. Only recently has such fine-scale understanding been gained and a dynamic model of the pathways leading to computational quantification of ATP release from red blood cells and its contribution to oxygen supply regulation has been completed [4]. Of course, when exercise is undertaken, enhanced levels of heat are also generated, in accordance with the second law. Heat itself is another factor modulating the cardiovascular response to physical exercise.

Insulin and metabolism

Insulin is a hormone, the levels of which influence the use of fuels towards either oxidation or storage. These fuels include carbohydrate, fatty acids, proteins and minerals. Following a meal hydrolysis of dietary carbohydrates liberates glucose which is absorbed. The increase in glucose concentration leads to insulin release with incretins playing an important role. Insulin facilitates the entry of glucose into all tissues (the availability of these receptors are insulin dependent, e.g. GLUT4) apart from brain and liver (non-insulin dependent glucose transporter), as illustrated in Fig. 1. On entry glucose is confined to the cell by hexokinase (which is activated by insulin) mediated Phosphorylation. Insulin also activates the enzymes in the glycogen synthesis pathway. In contrast falling plasma glucose is accompanied by cessation of insulin secretion (also accompanied by secretion of glucagon and other counter regulatory hormones) and this results in glycogenolysis.

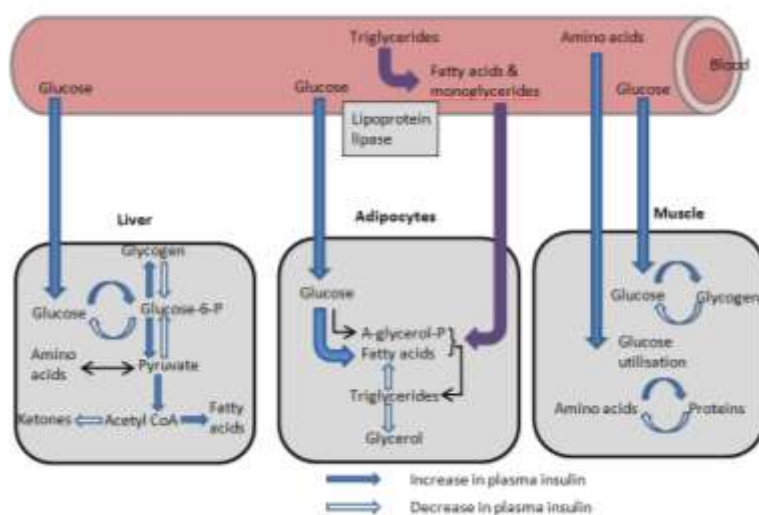


Fig: 1: Metabolic pathway of insulin

Glycogen is only stored in limited amounts in the liver. When this is saturated hepatic glucose is converted to fatty acids (via acetyl-CoA) and transported to the adipocytes within lipoproteins. Fatty acids are combined with glycerol (synthesised from glucose) and stored in the adipocytes as triglycerides, this anabolic action stimulated by insulin. Insulin also prevents use of triglycerides as an energy source by inhibiting intracellular lipases. Thus, fatty acid is an energy source via gluconeogenesis (facilitated by counter regulatory hormones) when insulin secretion is switched off.

Thus, it is clear that a balance of energy sources and utilisation at the cellular level are determined by the actions of insulin and counter regulatory hormones at multiple points.

Effects of disease

The laws of thermodynamics hold whether a person is healthy (implicit in the above) or diseased. In fact disease conditions can affect metabolism dramatically, ranging from the extremely rare premature ageing Hutchinson-Gilford Progeria syndrome [6] to the unfortunately common metabolic syndrome [7]. Also affecting cellular metabolism is type 2 diabetes, which is part of the metabolic syndrome. Type 2 diabetes is considered to be multi-factorial in aetiology with insulin resistance and β cell dysfunction being key factors. The role of genetic factors is undoubted; however, the part played by each of the associated candidate genes have been modest thus far with odds ratios ranging between 1.09 and 1.25. Awareness of the actions of insulin, insulin receptors structure and function and insulin resistance leads to some understanding of its pathogenesis and the role of therapeutic agents in current use.

The balance of energy sources and its utilisation by insulin and other hormones mentioned above has led to a variety of different medication strategies to manage diabetes 2. These are summarized principally in table 1. Derangement of this complex mechanism of control also opens the possibility of metabolic states such as diabetes and the metabolic syndrome.

Site of action	Action	Agents
Pancreas	↑ Insulin secretion	Sulphonylureas Meglitinides Gliptins, GLP1 agonists
Liver	↓ Glucose production	Biguanides Thiazolidinediones
Gut	Slow carbohydrate digestion	α -glucosidase inhibitors Biguanides
Muscle & Adipose	↑ Peripheral insulin sensitivity	Thiazolidinediones

Table 1: Type 2 Diabetes and the actions of therapeutic agents

Effectiveness of medication strategies: possible haemodynamics markers

For conditions such as atherosclerosis and cerebral aneurysms [8] the wall shear stress, that is the effect of fluid friction on the endothelial surface is a well-known indicator [9]. Fig. 1 shows that the haemodynamic system is also key in overall bodily metabolism and hence in metabolic syndrome / type 2 diabetes. Recent developments in CFD allow not only the local haemodynamics to be studied, but also erythrocyte behaviour and wall transport mechanisms. Alternative clinical methods to provide patient-specific data for haemodynamic simulations are IVUS, OCT, MRI and PET scanning [10]. An initial collaboration between engineers and clinicians is underway.

Conclusion

The clinical aim of this study is to identify possible clinical marker(s) in patient-specific treatment of the metabolic syndrome / type 2 diabetes. In this paper an integrated and fundamental understanding of human metabolism based on the principles of thermodynamics and the role of insulin, show that haemodynamics is key to that understanding, both for healthy and diseased states. Therapeutic agents for type 2 diabetes are summarised and an overall approach proposed to identify candidate clinical markers based on the local haemodynamics.

REFERENCES

- [1] Collins, M. W., Stasiek, J.A. & Mikielwicz, J. (2007) The laws of thermodynamics and *Homo sapiens* the engineer. In: J.A.Bryant, M.A.Atherton & M.W.Collins (eds.) Design and Information in Biology, Vol 2, International Series on Design and Nature, WIT Press: Southampton, UK, pp 179-204
- [2] Smith, C., *The Science of Energy*, The Athlone Press: London, UK, 1998
- [3] Mikielwicz, J., J.A. Stasiek, et al. (2005) The Laws of Thermodynamics: cell energy transfer. In: M.W.Collins, M.A.Atherton & J.A.Bryant (eds), Nature and Design, Vol 1, International Series on Design and Nature, WIT Press: Southampton, UK, pp 29-62
- [4] Goldman, D., Fraser, G.M., Ellis, C.G., Sprague, R.S., Ellsworth, M.L. & Stephenson, A.H. (2012) Toward a multiscale description of microvascular flow regulation: O₂-dependent release of ATP from human erythrocytes and the distribution of ATP in capillary networks. *Frontiers in Physiol.*, 3(7). doi: 10.3389/fphys.2012.00246
- [5] González-Alonso, J. (2012) ATP as a mediator of erythrocyte-dependent regulation of skeletal muscle blood flow and oxygen delivery in humans. *J.Physiol.*, 590(20):5001-13
- [6] Mehta, I.S., Eskiw, C.H., Arican, H.D., Kill, I.R. & Bridger, J.M. (2011) Farnesyltransferase inhibitor treatment restores chromosome territory positions and active chromosome dynamics in Hutchinson-Gifford progeria syndrome cells, *Genome Biol.*,12: R74
- [7] Alexander, C.M, Landsman, P.B., Teutsch, S.M. and Haffner, S.M. (2003) NCEP-Defined Metabolic Syndrome, Diabetes, and Prevalence of Coronary Heart Disease Among NHANES III Participants Age 50 Years and Older *DIABETES*, VOL. 52, MAY 2003
- [8] Cavazzuti, M., Atherton, M., Collins, M. and Barozzi, G., (2010) Beyond the Virtual Intracranial Stenting Challenge 2007: Non-Newtonian and flow pulsatility effects, *J. of Biomechanics*, 43 (13) : 2645- 2647
- [9] Pontrelli, G., König, C.S., Collins, M.W., Long, Q., Succi, S. (2011) Modelling wall shear stress in small arteries using LBM and FVM: influence of the endothelial wall profile, *Med. Eng. & Physics*, 33(7), pp. 832-839
- [10] Suo, J., McDaniel, M., Eshtehardi, P., Dhawan, S.S., Taylor, R.W., Samady, H., Giddens, D.P. (2011) 3D optical coherence tomography (OCT) — An investigation of intimal-medial thickness (IMT) and Wall Shear Stress (WSS) in a patient's coronary artery, In: *Computing in Cardiology*, 2011, September 18-21, 2011Hangzhou, China, pp. 217 – 219

Extensive experience of UK National Health Service T2diabetes clinics highlights the need for a convenient clinical marker which can be readily used to indicate the success or otherwise of alternative therapies. Such a marker would be of considerable clinical benefit and the research we are embarking on is to identify such.

Prima facie, we believe such marker(s) will be based on metabolic factors/agents and transport across the endothelial surface. Within that context the crucial concept in both cell and whole body metabolism is free energy, based on the Laws of Thermodynamics. Hence the paper. Also, current fluid dynamics cardiovascular studies point to variant scientific indicators based on endothelial wall shear stress.