Editorial

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Diabetes Medication Care and Characteristic of Metabolic Health and Disease

Abstract

From a biological view, most of the processes involved in insulin resistance, which drives the pathobiology of type 2 diabetes, are reversible. This theoretically makes the disease reversible and curable by changing dietary habits and physical activity, particularly when adopted early in the disease process. Yet, this is not fully implemented and exploited in health care due to numerous obstacles. This article reviews the state of the art in all areas involved in a diabetes cure-focused therapy and discusses the scientific and technological advancements that need to be integrated into a systems approach sustainable lifestyle-based healthcare system and economy. The implementation of lifestyle as cure necessitates personalized and sustained lifestyle adaptations, which can only be established by a systems approach, including all relevant aspects (personalized diagnosis and diet, physical activity and stress management, self-empowerment, motivation, participation and health literacy, all facilitated by blended care and health). Introduction of such a systems approach in type 2 diabetes therapy not only requires a concerted action of many stakeholders but also a change in healthcare economy, with new winners and losers. A "call for action" is put forward to actually initiate this transition. The solution provided for type 2 diabetes is translatable to other lifestyle-related disorders.

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Introduction

Current health care in the area of lifestyle-related diseases does not focus on reversal of the cause of the disease, but rather on controlling disease corollaries by manipulating biochemical pathways (gluconeogenesis by metformin, hepatic cholesterol synthesis by statins, insulin secretion by sulfonylureas, fatty acid housekeeping by PPAR agonists, etc.) [1]. A large repertoire of tools, technologies, and medicinal treatments has been developed for this purpose. Chronic disease care and (cardiovascular) risk management have been vastly improved thanks to these possibilities. However, we are running into the situation that disease care soon becomes too costly, with a number of stakeholders that either financially profit from the status quo or find the effort to change it too complicated [2]. Also, unbeneficial drivers in our healthcare economy maintain this situation, as only reductionist solutions can be patented. In the context of our current healthcare system, citizens become patients in the literal sense of the word: patiently undergoing treatments instead of playing an active role in their own health care [3]. In the end, this is an inefficient approach for treatment of the so-called "lifestyle related diseases," including metabolic syndrome, obesity, type 2 diabetes, and cardiovascular disease. Moreover, we now know that our lifestyle partakes in the pathogenesis of many other diseases [inflammatory diseases like rheumatoid arthritis, COPD, gastroesophageal reflux disease, osteoarthritis, neurological diseases like Alzheimer and multiple sclerosis, and specific cancers. Over the past 10 years, an integrated view on health and health care was developed, embracing health as a system (including systems biology concepts and technologies), the development of disease from health as a continuum and exploiting these assets toward "P4-medicine" (Predictive, Personalized, Preventive, and Participatory) [4]. The personalized aspect emerged from the possibilities to quantify the causal mechanisms involved disease predisposition (genetics) and development

(environment), while the participatory aspect related both to the health and medical data ownership and the need for patient citizens to take optimal control of all aspects of their own health, spanning all biopsychosocial aspects. In this article, we will focus and elaborate on type 2diabetes as an exemplary prototype of a lifestyle-related disease, but very similar concepts and approaches are valid for many other diseases [5]. The theoretical framework of P4 medicine and P4 health is now solid, but yet difficult to translate into daily practice of health care for a number of reasons, mostly related to conflicting stakeholder interest and cost of implementation. Some examples are emerging, but mostly in an experimental and costly setting. Type 2diabetes is also interesting as the disease is not only part of a continuum from health to comorbidities and preventable but also to a large extends reversible and curable with relatively simple means, once P4 or P6 health is implemented, as will be demonstrated below [6].

Metabolic Health and Disease

The metabolic state of patients with type 2 diabetes is routinely quantified in a symptomatic manner, i.e., by the fasting plasma glucose concentration (the acute symptom) and HbA1c (the accumulated symptom) [7]. Yet, these are the consequences of a complex network of interactions between food intake and fuel metabolism, involving multiple organs and biochemical pathways. For optimal metabolic health, each of these processes needs to function optimally [8]. We argue that effective treatment of type 2diabetes requires appropriate quantification of the multiple processes leading to disease itself, its progression, and its cure. In this context, it is important to note that type 2 diabetes is not a uniform disease. There are probably many subtypes with their own pathophysiology, born out of specific gene–lifestyle interactions. If this is the case, there is no optimal "one size fits all" treatment of type 2 diabetes. Each disease variant most likely requires its own therapeutic approach [9].

Systems Flexibility

Most of the metabolic processes that go awry in type 2diabetes have to function in a continuously changing environment (diet, infections, stress, temperature, exercise, etc.) where they strive to maintain internal homeostasis by adapting to these changes, usually in an hour–day timescale. Under chronic external stress (month–year timescale: high calorie diets, chronic inflammation), two major adaptation processes occur. On the one hand, the molecular physiology that regulates the acute stress response reactions accelerates to maintain homeostasis of the important parameters, possibly at the cost of other parameters. During caloric excess, plasma glucose, triglycerides, and inflammatory markers are initially maintained at normal levels, as a result of elevated concentrations of insulin, glucagon, and other regulatory mechanisms. However, prolonged caloric excess invokes adaptive processes like storage of excess calories in the form of triglycerides, which eventually may have negative consequences (obesity, ectopic adipose deposits, insulin resistance, inflammation, and eventually impaired insulin secretion). We call this phenotypic or systems flexibility. Disease onset occurs when and where one or more of these adaptive processes fail [10]. Importantly, diet and lifestyle play both a negative (caloric excess) and positive role: many nutrients serve specifically to optimize these flexibility processes. Already in 2002, the Diabetes Prevention Program demonstrated in a large 4-year study that, although metformin and lifestyle both were effective in maintaining fasting plasma glucose, the plasma glucose response to an oral glucose tolerance test (OGTT) (a core aspect of phenotypic flexibility) was more efficiently restored by lifestyle change than medication.

Role of Medication

The current pharmaceutical approach to diabetes care is to assist the patient in maintaining glucose, lipid, and blood pressure control. Metformin primarily decreases hepatic glucose production. Thiazolidinediones assist in fatty acid storage in adipose tissue, thereby increasing the use of glucose as energy source and reducing ectopic fat storage. Sulfonylureas stimulate insulin secretion, DPP4 inhibitors prolong the half-life of insulin-stimulating hormones, and exogenous insulin facilitates organ glucose uptake. Medication is prescribed depending on the stage and severity of the disease. Yet, none of these medications addresses the root cause of T2D and will thus not cure the patient. The extent to which insulin sensitivity

and/or action are compromised in each of these tissues may differ between patients. Therefore, the treatment strategy should be tailored to personal disease characteristics. For example, hepatic insulin resistance due to hepatosteatosis in a relatively lean subject may be due to impaired fatty acid uptake by subcutaneous fat or by excessive consumption of refined carbohydrates. Combining PPAR agonists with restriction of sugar (and alcohol) intake could be a beneficial "food-pharma" couple.

Conclusion

In this article, we provide evidence for the reversibility of insulin resistance and the remission of type 2 diabetes, specifically by diet and lifestyle. Complete cure may be achieved if beta-cell function is still appropriate and complications have not yet occurred. We demonstrate that T2D is a "systems disease" with multiple organs and processes involved and consequently deserve to be treated in a personalized manner, if necessary in a "personalized lifestyle-personalized medicine combination." Compliance to lifestyle change has been a major obstacle for implementation in health care, but the advancements in behavioral change technologies, health, health literacy, and personal health data valorization now may allow for a switch from a research setting to real-life socioeconomic implementation. Enough arguments and instruments are currently available to implement a lifestyle-based therapy for type 2 diabetes and other food-related lifestyle diseases and to extend this to a prevention and optimal health focused health care. Also, we argue that in doing so, an enormous economic gain will be achieved, which is well able to finance a lifestyle-based prevention and optimal health focused health care and economy. Since stakeholders, losses, and profits in this new economy will substantially differ from the current situation, the current healthcare industry will only slowly transit toward this new situation. Creative ways of implementation thus need to be explored. Ultimately, health data cooperatives may become the basis and drivers for this change, but this will take some time to develop into an economic reality. In the meantime, creative new "ecosystems" need to be explored that combine all necessary instruments for specific type 2 diabetes populations to be really effective. The goal would not only be to demonstrate its therapeutic efficacy but also and possibly more important to demonstrate that a new health economy that provides the services (coaching, ITC, foods, diagnostics, medication, all of these personalized and integrated) can become profitable while significantly reducing the net healthcare costs. Such ecosystems should preferably be regional, facilitating the simultaneous change of all relevant components if the "change system" to interact. This will allow community building, involvement of local healthcare centers, the local health and lifestyle-related economy, etc. The Chicago based south side diabetics project is a good example. The good message is that many early adopter activities, programs, and movements are already active in this area, covering parts of what is needed. A challenge will be to connect and integrate these into functional and flexible programs that can deliver "tailored systems solutions" depending on the personal and subgroup needs. The major challenge will be to fund these programs, at least to the point that they become self-sustainable. Here, sustainability does not necessarily imply a profitable service as such, but the identification of new natural funders, i.e., the entities that profit from the new systems. Besides the actual service providers, these can be governments, health insurance, employers, and investors. In other words, only a temporary funding of a transition phase needs to occur, once the architecture of such ecosystems is in place.

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Conflict of Interest

None

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