Abstract

This communication is an interesting and off-beat take on the concept of theranostics, as applied to diabetes care. It proposes the use of the term diabeto-theranostics, to define the combined use of diagnostic and therapeutic modalities, so as to create individualized or personalized treatment strategies in persons with diabetes. Historical examples such as the chlorpropamide challenge test and modern innovations such as genotyping are described. The rubrics of gluco-phenotype, endo-phenotype, metabolic phenotype, glucagon: insulin ratio, and adenosine monophosphate activated protein kinase (AMPK) status in planning glucose lowering therapy are explained. Novel concepts such as psycho-theranostics and electro-theranostics in diabetes are discussed.

Keywords: Diabetes, LADA, MODY, person centered care, type 2 diabetes.

Introduction

Theranostics is a modern field of medicine which combines diagnosis and therapy. A portmanteau, created from therapy and diagnostics, the word itself highlights a concept of portmanteau medicine, combining 2 scientific verticals. The first known example of theranostics is over 75 years old, when radioactive iodine (I-131) was used for both diagnosis and therapy of thyroid cancer.1 Currently, the term theranostics is used to describe interventions which simultaneously combine diagnosis and treatment.2 However, it also includes situations where sequential application of imaging and treatment modalities allows person-specific management.

Diabeto-theranostics

The term theranostics is commonly used in nuclear medicine and oncology. Here, we propose a new concept, diabeto-theranostics. Diabeto-theranostics is defined as the science which combines diagnosis of diabetes with specific therapy. While diabeto-theranostics may be used as a synonym for modern personalized or gene-based diabetes care, this concept is much older and more expansive than this.

Sulfonylurea challenge / therapy

In conventional diabetes care, such theranostic phenomena are well known. The chlorpropamide alcohol flush (CAF) was a provocative test, performed using a drug that was otherwise used for therapeutic purposes (chlorpropamide 250 mg). CAF positively (flushing) was found to be frequent in type 2 diabetes (who responded to therapy with chlorpropamide as well), and rare in type 1 diabetes (who needed insulin for treatment).3 This observation led to the informal use of the sulfonylurea challenge test, or glibenclamide tolerance test. This has been used historically to differential diagnose (and manage) type 2 diabetes. Many variants were used in diabetes practice. One method was to administer 2 or 4 tablets of glibenclamide (5 mg), and monitor glucose levels. A fall in plasma glucose, with or without symptoms of hypoglycaemia, suggested the diagnosis of type 2 diabetes, while lack of response to this stat dose implied autoimmune or insulin deficient diabetes. (Personal communication: Prof BK Sahay, Prof AH Zargar). Thus, the same molecule or drug was used successfully for diagnostic and therapeutic purposes.

Recently published literature has called for its resurgence in diagnosis of childhood diabetes.4 An intravenous bolus of glucose was administered to children with type 1 diabetes and neonatal diabetes, followed by an oral dose of glipizide. C-peptide levels increased after both glucose and glipizide in healthy controls, but only after glipizide in neonatal diabetes. There was no change in C-peptide levels in 2 of 3 antibody positive type 1 diabetes and 11 out of 12 antibody negative type 1 diabetes. Two children diagnosed as having type 1 diabetes demonstrated a small rise in C-peptide, suggesting a defect in glucose stimulated insulin secretion, rather than typical autoimmune dysfunction. Thus sulfonylureas, which are extensively used in therapeutics of diabetes, may have diagnostic relevance even today.
Gene-based therapy
The concept of personalized medicine, as applied to diabetology, may be considered as a type of theranostics. Genotyping for monogenic diabetes, such as neonatal diabetes and maturity onset diabetes of the young (MODY), allows institution of person-specific glucose-lowering therapy, based upon results of geno-diagnosis. Extensive research is available on the association of specific genotypes with development of type 1 and type 2 diabetes, response to various metabolic therapies, and mortality risk. A patent has recently been drawn for use of modern drugs such as the dipeptidyl peptidase (DPP4) inhibitor, linagliptin, in genotyped diabetes patients. However, in all the afore-mentioned examples, the diagnostic tools used are different from therapeutic strategies. Hence gene based therapy, in its current form, does not conform to the definition of theranostics. With our proposed definition (combining diagnosis of diabetes with specific therapy), however, gene based therapy becomes a perfect example of diabeto-theranostics.

Endophenotype based therapy
The term ‘endo-phenotype’, commonly used in genetic epidemiology and psychiatry, can be used in the context of diabetes as well. While phenotype means the sum of all external attributes of an organism (exophenotype), endo-phenotype implies genetic or ‘internal’ characteristics which are invisible to the unaided eye. These characters can be biochemical, endocrine, physiological, anatomical, cognitive or neuropsychological in nature.

Endo-phenotype, in diabetes care, includes the concept of gluco-phenotype, which is defined as the clinical and biochemical attributes, which allow characterization of the glycaemic status, understanding of the etiopathogenesis of dysglycaemia and planning of therapeutic strategies, in an individual. Gluco-phenotypes can be described as predominant insulin deficiency/ resistance, lean/ obese, predominant fasting / post prandial / combined glycaemia, with /without reversible medical/ surgical/ psychological/ obstetric precipitating factors. Accurate characterization of the gluco-phenotype, which is achieved by simply clinical and biochemical analysis, allows institution of person specific glucose lowering treatment.

However, endo-phenotype is a relatively more comprehensive framework, as it includes metabolic, genetic and other biomarkers. Endo-phenotype, in diabetes, can be taken to imply an in depth analysis of the person’s genotype, phenotype, and gluco-type, and their correlation with each other. Endo-phenotype based therapy means the use of this diagnostic information to plan personalized treatment strategies. The metabolic phenotype, which has been used to propose metabolic triage in type 2 diabetes, also overlaps the endo-phenotype.

Similar rubrics, the glucagon: insulin ratio, and adenosine monophosphate activated protein kinase (AMPK) activity, which have been used to classify glucose-lowering drugs, contribute to the relevance and robustness of the endo-phenotype. These rubrics are based upon the mechanisms of action of various glucose lowering drugs. They encourage matching of biochemical or endocrine abnormalities (which may be suspected clinically or documented through assays) with drugs which are known to correct them. For example, a person with high insulin: glucagon ratio may benefit from a sodium glucose cotransporter-2 (SGLT2) inhibitor, while someone with low AMPK activity may gain advantage from metformin.

Psycho-theranostics
As diabetes is a chronic disease, diabetes care is a long term, infinite process. Thus the concept of theranostics in diabetes care is bound to be different from that seen in acute or ‘curable’ illness. Diabetes being a multifaceted syndrome, theranostics may find utility beyond the biomedical domain of illness.

Psycho-theranostics may be defined as the science of using the same psychometric tool for either screening or diagnosis, as well as treatment of disease. One aspect of diabetes care is psychosocial health. Coping with diabetes is an important part of living with diabetes, and influences health in many ways. Perceived inability to cope with the syndrome may lead to diabetes distress, which in turn leads to suboptimal outcomes. Traditional used scales for assessing diabetes distress have been validated as diagnostic tools. A recently validated instrument designed to assess coping styles, the GlucoCoper, is an example of a psycho-theranostic tool. The GlucoCoper acts as a diagnostic, monitoring, and therapeutic tool, as well as an aid to therapy.
Electro-theranostics
Yet another example of theranostics, related to diabetes complication management, is the use of transcutaneous electric nerve stimulation (TENS) in diabetic neuropathy. While it is certainly an effective therapeutic modality, TENS can be used as a diagnostic and monitoring tool to objectively measure the threshold of sensation. It scores over conventional biothesiometry, which has limited role in screening and confirmation of peripheral neuropathy.

Summary
This communication highlights interesting facets of the use of theranostics in diabetology. The term diabeto-theranostics is defined as the combined use of diagnostic and therapeutic modalities, so as to create individualized or personalized treatment strategies in persons with diabetes. This article discusses various historical, current and futuristic aspects of theranostics in diabetes care. Both non-pharmacological and pharmacological theranostic interventions are described.

References