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New guidelines for metabolic targets in diabetes: clinician's opinion does matter

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Abstract Evidence-based medicine replaced eminence-based medicine as a way to manage unavoidable clinical uncertainty. Moving away from "one-size-fits-all" medicine, personalized medicine seemed to have the potential of tailoring therapies to subsets of patients. Despite the rapid progress in drug development for diabetes, it is still challenging to achieve good glycemic control in a substantial population. Different diabetes management algorithms have been proposed: most agree with a HbA1c target of <7.0 % for the majority of people with diabetes, except the American Association of Clinical Endocrinologists (AACE) that claims for a lower HbA1c target (<6.5 %). The recently released American guidelines on the treatment of blood cholesterol recommends moderate-intensity statin therapy for primary prevention for persons aged 40–75 years with type 1 or 2 diabetes and LDL-cholesterol levels between 70 and 189 mg/dl. The Eighth Joint National Committee recommends pharmacologic treatment in the population aged 18 years or older with diabetes, with a goal systolic blood pressure of lower than 140 mmHg and a goal diastolic blood pressure lower than 90 mmHg. There are differences and similarities among these recent guidelines for people with diabetes, with the main differences related to the level of the evidence. There are recommendations based on expert opinions (insufficient evidence or existing evidence unclear or conflicting) in almost all guidelines. The ultimate decision about care of a particular patient is left to clinicians, as the way to manage unavoidable guideline uncertainty: clinician's opinion does matter.

Keywords Guidelines · Diabetes mellitus · Metabolic targets

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Introduction

Each patient should receive the most appropriate care. This statement hardly can find an opponent. Eminence-based medicine has long relied on clinical experience and expert opinion for clinical decision-making. The seminal studies of the Nobel laureates Tversky and kahneman [1] of how people manage risk and uncertainty disclosed that people rely on a limited number of heuristic principles, which reduce the complex tasks of assessing probabilities to simpler judgment operations. While this attitude of the human mind is quite useful, sometimes it leads to errors.

Eminence-based medicine was therefore replaced by evidence-based medicine, which identifies important knowledge gaps and information needs, formulates answerable questions, and assesses the validity of evidence and results. As originally defined by Sackett and Rosemberg [2], evidence-based medicine indicated the ability to track down, critically appraise, and incorporate the rapidly growing body of evidence into one's clinical practice. On the other hand, evidence-based medicine must rely on inductive reasoning to draw conclusions about the effectiveness and feasibility of application of trial data (mean group data) to individual patients. As a corollary, doctors have to do everything possible to reduce the chance of error.

At the turn of this century, scientists began to realize the promise of the Human Genome Project, as a way to identify predisposition to disease and to tailor treatment to the individual [3]. Later, the term "personalized medicine" had the capacity to attract media attention, as genomic medicine seemed to be leading toward a reductionist view of life, where health and disease is determined primarily by genetic difference. Moving away from "one-size-fits-all" medicine, personalized medicine had the potential of tailoring therapies to subsets of patients based on their likelihood to respond to therapy or their risk of adverse events. The challenge is how to identify these patients, and deliver truly personalized care that maximizes benefit and minimizes harm [4]. In the real world of individual patients, eminence-based, evidence-based, and personalized medicine cannot abandon clinical judgment [5].

Diabetes: still far from the metabolic targets

Despite the rapid progress in drug development for diabetes, it is still challenging to achieve good glycemic control in a substantial population. The data from the National Health and Nutrition Examination Survey and the Behavioral Risk Factor Surveillance System over the 1999–2010 period show that 52 % of survey participants (adults with self-reported diabetes) achieved the hemoglobin A1c (HbA1c) target <7 % from 2007 through 2010 [6]. For blood pressure, 52 % of participants reached the <130/80 mmHg target, and 72 % fell below the less ambitious target of <140/90 mmHg. Finally, 56 % of participants reached the <100 mg/dl LDL-cholesterol target. Interestingly enough, the percentages of people with diabetes achieving the blood pressure and LDL-cholesterol targets increased steadily from 1999 to 2010, while those achieving the HbA1c target showed a slight decrease from the 56 % of the previous period 2003–2006. Quite surprisingly, type 1 diabetic people, who in theory would benefit more from lower HbA1c targets, present the worst performance, with percentages of 24 % for HbA1c <7 %, and 12.3 % for HbA1c <6.5 % (percentages based on 24,428 patients with type 1 diabetes in Italy in 2009) [7].

New guideline for metabolic health in people with diabetes

The prevalence of clinical guidelines is very unlikely to decrease, also considering that about half of the major recommendations in guidelines become outdated in approximately 6 years. Management of hyperglycemia has become increasingly complex: it involves now at least 12 different classes of glucose-lowering agents in the U.S., and is increasingly costly, resulting in over $18 billion in annual expenditures [8].

HbA1c

Different diabetes management algorithms have been proposed [9–11], which have similarities and differences: however, most agree with a HbA1c target of <7.0 % for the majority of people with diabetes, with the exception of the American Association of Clinical Endocrinologists (AACE) [9] which claims for a lower target (HbA1c < 6.5 %), if safely achievable. More or less stringent goals are suggested for selected individual patients, on the basis of the safe achievement of the target (HbA1c ≤ 6.5 %) or for patients with concurrent illness and at risk for hypoglycemia (HbA1c between >6.5 and <8 %). Once again, clinical judgment remains paramount in decision. Although not strictly linked to metabolic targets, some inconsistency is present in diagnostic recommendations: for the American Diabetes Association [11], for example, people with HbA1c value between 5.7 and 6.4 % constitute a category at increased risk of diabetes (prediabetes), while for the World Health Organization [12] there is currently insufficient evidence to make any formal recommendation on the interpretation of HbA1c levels below 6.5 %. Moreover, providing specific targets for diagnosis has limitations which are also acknowledged by ADA: "risk is continuous extending below the lower limit of the range (5.7 %) and becoming disproportionately greater at the higher end of the range (6.5 %)." Perhaps time has come for clinicians to use multiple sources of information to assess glycemia, including fructosamine and glycated albumin, as performance of combination testing was better than HbA1c alone for the diagnosis of incident diabetes [13].

LDL-cholesterol

The recently released 2013 American College of Cardiology/American Heart Association (ACC/AHA) guideline [14] on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults recommends moderate-intensity statin therapy for primary prevention for persons aged 40–75 years with type 1 or 2 diabetes and LDL-cholesterol levels between 70 and 189 mg/dl (*level A*); high-intensity statin therapy may reasonable, unless contraindicated, for those diabetic patients with an estimated 10-year cardiovascular risk ≥7.5 % (*expert opinion*). High-intensity statin therapy lowers LDL-cholesterol level by approximately ≥50 % on average and can be obtained with atorvastatin (40–80 mg daily) or rosuvastatin (20–40 mg daily). Moderate-intensity statin therapy lowers LDL-cholesterol level by approximately 30 to <50 % on average.

Table 1 Recent recommendations by Scientific Associations for metabolic targets in people with diabetes

	HbA1c (%)	LDL-cholesterol (mg/dl)	Blood pressure (mmHg)
ADA, 2014	<7 %, for many patients	<100, without CVD <70, with CVD	<140/90
(level of evidence)	B	B	B
AACE/ACE, 2013	<6.5 %, for healthy patients	<100, moderate risk <70, high-risk	~130/80
(level of evidence)	Expert opinion	Expert opinion	Expert opinion
JNC8, 2014	–	–	<140/90
(level of evidence)			E
ACC/AHA, 2013/2014	–	No target level High statin: estimated 10-year CVD risk ≥ 7.5 %	–
(level of evidence)		E	
ESC/EASD, 2013	<7 %	<100, high risk <70, very-high risk	<140/85
(level of evidence)	C†	A	A
	Prevention of CVD		

ADA American Diabetes Association, *AACE* American Association of Clinical Endocrinologists, *JNC8* Eight Joint National Committee, *ACC* American College of Cardiology, *AHA* American Heart Association, *ESC* European Society of Cardiology, *EASD* European Association for the Study of Diabetes, *CVD* cardiovascular disease, *level of evidence B* supportive evidence from well-conducted cohort and case–control studies, *level of evidence E* insufficient evidence or evidence unclear (expert opinion). *C*† Consensus of opinion of the experts, *level of evidence A* data derived from multiple randomized clinical trials or meta-analyses, ~ approximately

Blood pressure

The Eighth Joint National Committee (JNC 8) released the 2014 evidence-based guideline for the management of high-blood pressure in adults [15]. In the population aged 18 years or older with diabetes, pharmacologic treatment should be initiated at systolic pressure (SP) of 140 mmHg or higher, or diastolic pressure (DP) of 90 mmHg or higher, and treat to a goal SP of lower than 140 mmHg and a goal DP lower than 90 mmHg (*expert opinion*). The panel also recognizes that goals of lower than 130 mmHg for SP and lower than 80 mmHg for DP are commonly recommended for adults with diabetes and hypertension, without sufficient evidence to support these lower goals.

The recent lipid and blood pressure guidelines have generated much debate within the scientific arena, from the peril of global statinization [16], to the need to harmonize the many cardiovascular risk guidelines and recommendations, to the need of randomized clinical trials that looks at the real-world generalizability [17].

Difference and similarities

There are differences and similarities among these recent guidelines for people with diabetes [9–11, 14, 16]. As indicated in Table 1, the main differences relate to the level of the evidence, which may vary sharply: for blood pressure targets, ESC/EASD guidelines used the highest level (A), while the JNC8 used the lowest level (E). There are recommendations based on expert opinions (insufficient evidence or evidence is unclear or conflicting) in almost all guidelines, including the HbA1c target of ≤7.0 % for the prevention of CVD (ESC/EASD), high-intensity statin therapy for people with an estimated 10-year CVD risk ≥7.5 % (AHA/ACC), and the blood pressure target <140/90 mmHg (JNC8). All the recommendations released by ACCE/ACE are based on expert opinion, as "participating clinical experts utilized their judgment and experience" [9].

Conclusions

Failure to treat to target, or prescribing that is not concordant with guidelines are being referred to as clinical inertia [18]. Medicine is an applied science and, as such, complete certainty in clinical medicine is unattainable. Moreover, the same science can be applied in different ways by different doctors. This may be one reason why the ACC/AHA guidelines no longer emphasize the achievement of LDL-cholesterol target in diabetes: taking a statin may be enough, as this has been shown to reduce cardiovascular outcomes.

Guideline recommendations impact on thousands of general practitioners and specialists, and hence on millions of diabetic patients. Clinicians should have confidence in the recommendations: the fact that recommendations for some metabolic targets in diabetic patients are based on expert opinions is not necessarily a harm, as the skill of the physician cannot be codified into any rigid or mathematical formula. Unfortunately, we do not have studies available for every question we might ask, and some questions cannot be answered. This is acknowledged in guideline

recommendations that are said to be not a substitute for clinical judgment [16], as the ultimate decision about care of a particular patient must be made by in light of the circumstances presented by that patient: situations might arise in which deviations from these guidelines may be appropriate [14]. At very last, the way to manage unavoidable guideline uncertainty is left to clinicians: clinician's opinion does matter.

Conflict of interest The authors declare no conflict of interest.

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