Cardiometabolic Risk: Current Perspectives and Future Aims

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As new data emerge and diabetes treatment strategies are modified, the priorities that are associated with diabetes management tend to shift. Clinicians are beginning to take a fresh look at diabetes care goals and are considering personalized approaches versus the standardized care methods. Cardiometabolic risk assessment has become a key component to these new management strategies. Many of these risk factors can be alleviated with lifestyle modification and diet adjustments. Over the past decade, trial data have broadened our understanding of cardiometabolic risk as it applies to diabetes and other health issues. For this reason, a new focus on cardiometabolic risk and prevention is emerging.

According to ADA standards of care in diabetes, the target HbA1C for adult patients with type 1 and type 2 diabetes mellitus should be <7.0% for macrovascular risk reduction [ADA Standards of Care. *Diabetes Care* 2010]. Craig Williams, PharmD, Oregon Health & Science University School of Medicine, Portland, OR, discussed the current clinical goals for cardiometabolic risk reduction, based on trial data. Cardiometabolic risk reduction involves HbA1C levels, blood pressure (BP), low-density lipoprotein (LDL) cholesterol, and, potentially, aspirin therapy. Current recommended clinical goals are shown in the table below (Table 1). The American Diabetes Association, American Heart Association, and American College of Cardiology guidelines concur with these recommendations and have updated their protocols accordingly. Some data suggest that more aggressive targets are not warranted for CVD reduction [The ACCORD Study Group. *N Engl J Med* 2010].

Table 1. Clinical Goals for Cardiometabolic Risk Reduction

HbA1C (%)	~7%
Systolic blood pressure (mm Hg)	~130 mm Hg
LDL cholesterol (mg/dL)	<100 mg/dL with statin therapy
Aspirin	Use in higher risk patients with diabetes (men aged >50 years plus another CVD risk factor and women aged >60 years plus another CVD risk factor)

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The issue of standardized versus personalized diabetes care goals has been a point of contention among diabetologists and primary care physicians alike, and how to best personalize treatment parameters, such as HbA1C, BP, and lipids, remains unclear. Patrick J. O'Connor, MD, HealthPartners Research Foundation, Minneapolis, MN, discussed potential challenges and advantages that are associated with the personalized treatment approach. Standardized guidelines focus on maximizing the percentage of patients who reach evidence-based goals, while personalized guidelines emphasize clinical interventions that best minimize personal or population macrovascular and microvascular complication risks.

Standardized care goals that are derived strictly from evidence-based medicine are not without their flaws, as Dr. O'Connor pointed out. Randomized clinical trial data are often based on patients who differ from the real world in relation to severity of illness, adherence, or access to clinical care.

Standardized care goals that are derived from observational studies may not accurately determine optimal ranges of A1C, BP, and lipids. For example, epidemiological data suggest that any A1C level over normal increases risks of macrovascular complications, but recent clinical trials have not shown reduced cardiovascular mortality when patients with elevated A1C are aggressively treated to normal A1C. In the world of clinical intervention, more is not always better. Beyond a certain point, aggressive treatment may not have a favorable impact on outcomes. In certain circumstances, patients may benefit from more moderate goals.

Prioritization of treatment strategies that are based on individual absolute risk and benefit may be the preferred method moving forward. Such an approach is based on an obvious fact—not all evidence-based care recommendations have equal benefit to a given patient at a given time. The goal of prioritized care is to identify which clinical interventions have the most benefit while taking into account patient preference.

Adoption of a prioritized approach to care may reduce polypharmacy and the cost of care while maintaining or improving good clinical outcomes. However, such an approach will require modification of accountability measures to focus more on risk reduction rather than achievement of specific standardized goals in the clinical "silos" of glucose, BP, or lipid control, for example.

In order to streamline this personalized approach, electronic tools may facilitate tailored decision-making. Richard W. Grant, MD, Massachusetts General Hospital, Boston, MA, discussed personalized diabetes care in the setting of electronic software. The algorithms

within such software could be tailored to the individual patient's preferences and could reflect the philosophy of the clinician. Health IT tools have the potential to foster patient-physician collaboration through online web portals and allow implementation of personalized decision-making algorithms without adding to the treatment burden. Additionally, fast-track tools may generate letters and treatment recommendations between visits at the clinician's discretion, keeping the lines of communication open throughout the duration of treatment. In a study by Grant and colleagues that evaluated the effect of the personalized approach using electronic health record software in diabetic patients, patients took an active role in their diabetes management, and a diabetes care plan was developed based on their individual risks and needs. Those in the intervention arm demonstrated an increase in active medication management compared with control ($p<0.001$) [Grant RW et al. *Arch Int Med* 2008]. The use of electronic tools may assist clinicians in the transition from standardized to personalized care.

Cardiometabolic risk assessment is becoming an integral part of diabetes care strategies. Clinicians are beginning to modify their methods of treatment, based on risk profiles. The medical community has become more aware of the impact of lifestyle and other factors on diabetic management. New treatment strategies, such as personalized goals and care plans, are on the horizon and may influence the global problem of obesity and cardiometabolic syndrome.

Fructose Consumption and Obesity

Another issue that merits discussion is the role of fructose consumption in cardiometabolic risk. Kimber Stanhope, PhD, University of California, Davis, CA, provided information about the metabolic mechanisms that are associated with fructose and how they apply to cardiometabolic risk. Studies have shown that diets that are high in fructose induce symptoms of the metabolic syndrome in animals [Bizeau ME et al. *Metabolism* 2005; Havel PJ et al. *Nutr Rev* 2005; Le KA et al. *Curr Opin Clin Nutr Metab Care* 2006; Wei Y et al. *J Nutr Biochem* 2007]. In animals, diets that are high in fructose have been found to increase *de novo* lipogenesis, dyslipidemia, insulin resistance, and obesity. However, few studies are available with regard to the impact of fructose on these metabolic components in humans.

A recent study by Stanhope and colleagues investigated the effect of fructose consumption on body composition, *de novo* lipogenesis, lipids, and insulin sensitivity compared with glucose in overweight/obese humans. Over the course of 10 weeks, patients consumed either fructose- or glucose-sweetened beverages, providing 25% of energy requirements. Two of the 10 weeks were part of an inpatient intervention period, allowing for comparisons under well-controlled metabolic conditions (with a coordinated energy-balanced diet), and 8 of the 10 weeks were part of an outpatient intervention period that included an ad libitum diet along with the predetermined beverage component of the diet. All patients were aged 40 to 72 years with a BMI of 25 to 35 kg/m^2 and stable body weight 6 months prior to study participation.

Visceral adipose tissue accumulation increased significantly in patients who consumed fructose versus glucose at 10 weeks ($p<0.01$) suggesting differential effects of fructose versus glucose on regional adipose distribution. Consumption of fructose led to dyslipidemia, but lipids did not appear to be influenced by the consumption of glucose. Increased levels of postprandial triglycerides, fasting and postprandial apoB and LDL, fasting small dense LDL, and oxidized LDL were observed in the fructose group versus no change in the glucose group. Fructose consumption was also associated with deteriorated glucose tolerance and insulin sensitivity. At 10 weeks, insulin sensitivity was decreased by 17% in the fructose group [Stanhope KL et al. *J Clin Invest* 2009].

It is important to note that foods are generally sweetened with sucrose (which is 50% fructose/50% glucose) or high-fructose corn syrup (which is 42% to 55% fructose/remaining % glucose) rather than pure fructose or pure glucose. Therefore, more studies are needed to determine the effects of consuming diets that are high in sucrose or high-fructose corn syrup and to determine the level of dietary fructose that can be consumed without adverse metabolic effects.

Julie Miller-Jones, PhD, St. Catherine University, St. Paul, MN, emphasized the importance of differentiating between fructose sources, such as fruits and vegetables, versus added fructose that is ingested in the form of corn syrup, high-fructose corn syrup, and agave.

Some of the trends that are noted with sweetened beverage consumption may be the result of increased caloric intake. In a study by Ludwig and colleagues, the consumption of sweetened beverages predicted weight gain in children [Ludwig et al. *Lancet* 2001]. Investigators concluded that weight gain may have less to do with the type of sweetener and may be more closely related to excess calories. In an evidence-based review by Dolan and colleagues, the physiological effects (higher triglycerides and weight gain) that are observed with very high fructose intake were not observed with fructose intake that approached the 95th percentile [Dolan et al. *Crit Rev Food Sci Nutr* 2010].