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Instituting Modest Therapeutic Lifestyle Changes for Those at High Cardiometabolic Risk in Primary Care

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This podcast is in two parts. The longer part, which is this first part, will be the justification and scientific support including recent clinical trial for instituting modest life style changes. And the second shorter part of this podcast will be examples of these modest life style changes.

PART 1
Patient noncompliance with therapeutic lifestyle interventions is among the most impactful issues in preventive endocrinology and cardiology. Such is the dilemma many of us find ourselves with invoking meaningful lifestyle changes for ourselves and our American Indian/Native Alaskan patients in the current era of blood lipid altering drug therapy. Most clinicians are fully aware that therapeutic lifestyle changes (TLC) most often underachieve blood lipid and lipoprotein target goals [e.g., TG <150 and LDL-C <100 mg/dl]. Much is the same with adherence to TLC in achieving lasting body weight reductions. One of the longest standing statin promotional advertisements still reads to this day “When diet and exercise fail - meet another candidate for lipid lowering therapy.” It’s almost subliminal that we fail before we start. Indeed, TLC often fails to achieve more aggressive laboratory goals – but most often does not fail to reduce cardiometabolic risk. Excepting those with major heritable lipid and metabolic issues, a disordered lifestyle is most probably responsible for the majority of lipid and metabolic disorders we see in the clinic. If we look at TLC outcomes with regard to cardiometabolic disease, particularly reduction in diabetes risk, there are a plethora of very beneficial physiological changes which occur with or without significant changes in either LDL-cholesterol or body weight. The point is that small incremental changes in lifestyle habits are clinically quite beneficial and this *frame-of-reference* has been lost merely because the patient’s modest lifestyle changes are not perceived to be sufficient to reach laboratory-driven targets. I am in no way disregarding the more aggressive and holistic lifestyle changes for those who are motivationally ready to change but there are options for those who are much more ambivalent and otherwise not ready for a complete lifestyle makeover.
The advent of at least seven classes of drug therapies to manage dyslipidemia, for example, has for many providers created a rather convenient but evidence-based defense for spending less time on more thorough teaching of dietary and physical activity behaviors. To be sure, the level and magnitude of TLC intervention to aggressively lower LDL-cholesterol for many requires gladiator-level commitment to achieve current LDL-C target thresholds.
Here is a question for us all. Is it not our overall clinical and public health mission to reduce risk of cardiometabolic disease? And if so, are there not metabolic mechanisms by which lifestyle changes interact to do just this – many of which are not uniquely married to blood lipid or even body weight changes?

We all are by now are very well aware of the impressive Diabetes Prevention Program (DPP) outcomes. Yet this near 60% reduction in new onset diabetes occurred with a mere 5% weight loss despite the 7% targeted goal at the beginning of the study (1). And these outcomes were achieved with very modest dietary intervention and approximately just 1000 kcal of exercise a week, even though at the onset of this study they were to achieve at least 1200 to 1500 kcal of exercise per week. The DPP Outcomes Study reinforced this success at 10 years of follow up with a 34% decreased incidence of diabetes compared with controls (2). And in addition a recent 20-year follow-up analysis of the Da Qing Chinese Diabetes Prevention Study using TLC to manage diabetes risk, indicated that the TLC group had a 51% lower incidence of diabetes during the active intervention period and a 43% lower incidence controlled for age (3). In other words, life style changes do work. These results were also attained with very modest changes in blood lipids and body weight. If a patient is only able to add 9 or 10 miles a week of walking, that is about 1.2 miles/day to their weekly activity they have essentially expended the same weekly energy expenditure as those who completed the DPP and other diabetes prevention studies with impressive results.

The "Pleiotropic" Effects of Therapeutic Life Style Changes: A Brief Look at the Evidence. And what I mean by pleiotropoic – I mean the secondary effects; in many cases these would be considered primary metabolic physiologic effects.

There are a litany of core metabolic changes by which positive changes dietary and physical activity behavior can improve cardiometabolic health including but not limited to anthropometric and blood lipid changes. What I mean by anthropometric changes, I mean body fat changes. This concept of TLC pleiotropy is not new. One of the most cogent examples of evidenced-based TLC pleiotropy is the response to the Mediterranean diet therapy for which there are many elements of this diet congruent with AI/AN lifestyles. The Mediterranean diet is one of the most studied dietary regimens to combat cardiovascular metabolic disease and it represents a "whole" dietary pattern in that it emphasizes good sources of carbohydrates (whole grains), fats (unsaturated plant oils and omega-3 fatty acids), and proteins themselves (nuts, legumes, fish, and poultry) and also an abundance of fruits and vegetables; and minimal intake of refined grains, sugar-sweetened beverages, and red meat. Katherine Esposito of the Second University of Naples demonstrated significant increases in insulin sensitization, improved arterial function and decreases in inflammatory markers, such as CRP, IL-6, IL-7, and so on. Now, Katherine Esposito has no less than about 30 papers in the literature and is probably the top of the academic ladder in researching the Mediterranean Diet. More recently Esposito demonstrated that prolonged adherence to a Mediterranean style diet pattern, with or without caloric restriction, in 192 overweight and obese men is associated with significant amelioration of multiple risk factors, including a better cardiovascular risk profile in terms of lower blood pressure, lower cholesterol and triglyceride and higher HDL-cholesterol; also reduced oxidative stress (less iso-8-PGF2*α*), and improved insulin sensitization and increased adiponectin levels (4b).

Olive oil and red wine antioxidant polyphenols transcriptionally inhibit endothelial adhesion molecule expression, thus partially explaining the athero-protection from these selected nutrients in Mediterranean and other dietary regimes (5). Esposito and coworkers have shown in two separate published trials a positive effect of the Mediterranean diet on reversal of the metabolic syndrome as well as its utility

ameliorating features of fatty liver in obese patients with insulin resistance and diabetes (6). A Mediterranean diet is not as stringent as very low-fat or very-low carbohydrate dietary interventions but can still reverse these hepatic and metabolic syndrome features.

In 2006, myself, researchers at Duke University and the Mayo Clinic conducted a trial where 19 weeks of TLC; what we actually used was about 1200 kcal/week of aerobic exercise (equivalent to about 12 – 13 miles/week of walking) and decreased energy intake in 37 overweight insulin resistant patients. And this regime showed significantly greater efficacy in improving insulin sensitivity, LDL particle number reduction, and fasting glucose compared to 30 mg of pioglitizone (or Actos) per day (7). Such findings are not isolated discoveries with over 170 published TLC efficacy trials published since 2000.

Lastly and perhaps most provocatively Mediterranean dietary qualities have been shown to reduce the incidence of new onset diabetes. Savado and others demonstrated a 52% decrease in the incidence of new onset type 2 diabetes in a randomized trial in 418 nondiabetic subjects aged 55-80 years of age as part of the PREDIMED study in Spain (8). What was remarkably noteworthy in Savaldo's study was that diabetes risk reduction occurred in the absence of significant changes in body weight or physical activity for that matter.

Modest Increases in Physical Activity are Beneficial

Exercise is not generally considered primary therapy for lipid disorders, especially in the current era of lipid-altering drug therapy. This is unfortunate, because physical activity of appropriate quality and quantity can clearly reduce cardiometabolic risk through nonlipid mechanisms. Exercise can also induce significant favorable changes in the lipoprotein profile only partly related to changes in adiposity. Bill Kraus and others from Duke University was among the first to show in a well controlled trial, comparing various weekly volumes and intensities of physical activity on lipids and lipoproteins, that regular exercise with minimal weight change has broad beneficial effects on the lipoprotein profile – even without changes in total cholesterol and Friedewald predicted LDL-C (9). Kraus demonstrated that moderate volumes of intensities of exercise, for instance walking about 12 miles per week at only 40-55% of aerobic capacity, can significantly reduce nuclear magnetic resonance spectrometry-measured LDL-particle number. In other words, NMR measured LDL-C particle number which is sort of a new way to look at more directly LDL burden. Okay, he looked at LDL-particle number when total cholesterol and Friedewald-predicted LDL-C remained unchanged. So LDL-particle number was reduced significantly without much of a change at all in the Friedewald-predicted LDL-C Such patients on a return clinic visit would be considered unresponsive to exercise therapy when a conventional lipid profile was used to score the patient's progress. LDL particle-number has gained much clinical trial support in recent years as a better predictor of cardiovascular events than LDL-cholesterol (10) as we had said earlier.

Improved arterial endothelial function is also thought to be one of the primary mechanisms responsible for reduced CVD disease morbidity and mortality (11). And it does not take a whole lot of exercise to improve arterial function. Numerous trials have

demonstrated improvements in arterial endothelial function with sufficient exercise training (12, 13). Dietary elements such as omega-3 fatty acids therapy (that is fish oil therapy), walnuts, and even olive oil have also been shown to significantly improve endothelial function and reduce postprandial lipemia (14,15). Postprandial lipemia also adversely affects arterial function, that means after a given meal what your triglycerides do in the next 6 to 12 hours. When postprandial triglyceride rich lipoproteins are significantly elevated, especially after a fat-rich meal, arterial walls are exposed to a variety of atherogenic lipoproteins (e.g., IDL or intermediate density lipoproteins) and there is a transient reduction in arterial function during this time. Single 35 - 40 minute exercise sessions, for example a 40 minute moderate pace walk, can significantly reduce postprandial triglyceride levels (16). This has been shown by numerous investigators.

Similar Mechanisms as Metformin (Biquanid) and the Glitizones (eg. Actos)

Now we also know that modest lifestyle changes, particularly exercise, act through very similar mechanisms as Metformin and the Glitozones, such as Actos, in other words diabetes medicines. Both moderate and intensive exercise bouts utilize similar metabolic mechanisms as these several drug classes, [the Biquanides (Metformin) and Thiazolidinediones (TZD's) (pioglitizone, rosiglitizone)] but without many of the side-effects, such as fluid retention of the glitizones. The value of brief acute bouts of physical activity, e.g. 2-5 minute intentional bouts of exercise at moderate intensities activate AMP kinase, glucose transport mechanisms, and insulin signaling helping to reduce cardiometabolic risk. Each intentional walking step is an AMP kinase activator (AMP-activated protein kinase is an enzyme that works as a fuel gauge which becomes activated during physical activity) which works similarly to glucophage and the PPARγ medicines we use in diabetes care work (17). Well engineered step-filtered pedometers measure these insulin sensitizing muscular contractions, that is walking steps, are very helpful in terms of measuring objective outcomes for reducing cardiometabolic risk. Both aerobic and resistance exercise training improve insulin sensitivity and glucose transport mechanisms which help to improve cardiometabolic health and are involved in deterring diabetes in prediabetic subjects. Perhaps the most promising of the metabolic mechanisms physical activity has to offer is it's ability to upregulate PPARδ (delta) receptors in skeletal muscle (18, 19). PPARδ receptors are intimately involved in fatty acid transport, inflammation, and increased HDL-C – essentially improving multiple aspects of the metabolic syndrome. Future development of diabetes drugs will target PPARδ receptors essentially mimicking the many benefits of exercise. There is also emerging evidence from investigators here at Duke University that exercise training can reverse skeletal muscle mitochondrial abnormalities from lipid overload induced by high fat load diets and inactivity (20).

Is It the Weight Loss or Physical Activity Itself that is reducing the risk?

In one of the most elegant clinical exercise science reviews recently published Richard Telford, physiologist at the University of Melbourne, revealed that the scientific literature indicates consistent findings of strong associations of physical activity (PA) with mortality and with morbidity associated with type 2 diabetes, <u>after</u> controlling for obesity

and other potentially confounding factors (21). Collectively, these findings indicate that low PA is not just a predictor, but a direct cause of metabolic dysfunction and the morbidity and mortality associated with diabetes. Considering the many cellular mechanisms that can help explain this - this finding is not difficult to justify. By contrast, Telford argues there is little evidence that overfatness and obesity (adjusting for any effect of reduced PA) actually cause diabetes. Observational studies suggest that obesity, including viscerally sited obesity as in the abdomen, is most appropriately categorized as a marker or predictive risk factor for T2D, although, in contrast to PA, several studies were not able to detect any significant correlation after controlling for PA. The findings are consistent with the premise that PA is of direct benefit, perhaps even essential, to preventive and curative medicine in relation to insulin resistance and T2D. This takes nothing away from weight loss programs. We know that anytime you add fat weight you do decrease insulin sensitivity. So this is not to say that we don't need to lose weight but perhaps that's not the only outcomes measure. It might be a better outcomes measure to be looking at the behavior itself, which in this case is physical activity. In support of Telford's argument Tim Church of Pennington Research Institute in Louisiana, investigation of 2316 men with diabetes over 16 yr which found that low-fit individuals were at 2.7 times the risk of dying of CV disease compared with the normal-weight men of high fitness, irrespective of whether they were of normal weight, overweight, or obese (22). Studies on Pima Indians corroborated this trend of observing a reduction in new onset diabetes with physical activity intervention with some independence of changes in BMI or body weight (23).

Lastly, Lopez-Soriano and colleagues in Spain and France who have focused their work on exercise induced PPAR nuclear receptor activation in both muscle and adipose tissue, cogently argue that physical activity is afforded very little attention in recent studies and reviews evaluating the link between insulin resistance, inflammation and obesity (25). They insist that physical activity is a potentially confounding factor which has been overlooked by many if not most in attempting to understand the role of obesity in diabetes risk reduction.

So the key point here is that physical activity helps reduce risk by reducing body fat and curbing weight regain after weight loss but the important message here is that PA operates through other mechanisms which are not uniquely married to weight loss. Just get your patients to move!

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