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Review Article

Exploring the Potential to Extend Productive Lifespan in Nondiabetics through Maintaining Optimal Insulin Sensitivity: Amelioration of an Abated Version of the Metabolic Syndrome

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ABSTRACT

Objectives: An inadequate metabolic response on the part of blood glucose to the usual or even augmented circulating levels of insulin is broadly referred to as "insulin resistance" (IR). IR has been associated with developing a collection of biological perturbations recognized as metabolic syndrome, a less-than-optimal IR status with aging is prevalent worldwide in the modern nondiabetic population due mainly to current poor nutritional practices.

Material and Methods: This phenomenon is explored using two different surrogates representing the strength of IR (serum fasting blood glucose and the ratio triglycerides/high-density lipoprotein cholesterol) as well as two different means to gage aging (chronological age and declining glomerular filtration rate over the lifespan).

Results: Establishing an important role in general health for what seem to be trivial but persistent stages of IR in the eyes of most observers today is important since it would provide early incentives to develop safe, convenient preventive measures to slow the aging process and lengthen meaningful lifespan.

Conclusion: Ultimately, the objective is to maintain the body in optimal shape by reducing IR throughout aging. This may help mitigate all sorts of metabolic disorders, including infectious processes occurring in one's lifetime.

Keywords: Lifespan continuum of risks, Metabolic syndrome, Aging paradox, Metabolic factors in insulin resistance, Insulin resistance, Biological aging, Quality of life accomplishment procedures

INTRODUCTION

Toward the end of the 20th century, we raised the prospect that even mild to modest levels of "insulin resistance" (IR)[1], the principal driving force behind type 2 diabetes mellitus (T2DM)

1 Non-optimal insulin functioning (sensitivity) regarding its actions particularly upon glucose metabolic events in the muscles, fat, liver, and pancreas. The eventual compensatory responses to IR commonly result in both elevated circulating glucose and insulin concentrations over time.

and the ubiquitous metabolic syndrome (MetS),[1-3] might play a significant adverse role in overall health and the "natural" biological aging phenomenon even in average fit, nondiabetic individuals.[4-8] Our purpose is to "determine if the slight intensification of IR and/or its associated metabolic risk factors over the lifespan of most nondiabetics is great enough to reduce general health status and accelerate aging pathology"[4-8] and to ascertain if the presence of diagnosed metabolic disorders, for example, T2DM and/or MetS, can assure enough potency of IR to produce significant, adverse aging-related trends.

The mild to moderate presence of IR and its accompanying risk factors have been suggested to hasten aging in aging nondiabetics over the lifespan.[9-11] Evidence in volunteers that the appearance of "survivor bias" in the elderly can be linked to a weakened IR status is also somewhat reassuring of such a possible happening.[9-14][2]

The goal is to analyze a novel version of the aging process (age-related renal estimated glomerular filtration rate [eGFR] decline in addition to chronological age)[15-22] and employ another novel but less popular surrogate for IR (ratio triglyceride/high-density lipoprotein [HDL]-cholesterol in addition to fasting blood glucose [FBG]).[23-26] The utilization of lifestyle improvements in dietary and exercise regimens, as well as proper use of natural dietary supplements and pharmaceuticals, enhance insulin sensitivity and mitigate manifestations related to MetS[27-30] peH.

MATERIAL AND METHODS

Clinical material

The clinical materials for this study came from Integrative Health Technologies, Inc., a Clinical Research Organization in San Antonio, Texas, USA. The Longitudinal Database of Medical Biomarkers includes multiple dual energy X-ray total body scans (DEXAs) and thousands of fasting blood chemistry measurements. The data were obtained from study participants representing all 50 States. All measures were taken to ensure that the subjects involved in the present study were essentially "normal volunteers" after historical health matters were considered. In short, the volunteers were relatively healthy, nondiabetic individuals. Many values in this single-center and observational cohort study were expected to fall in commonly accepted "normal" ranges. Linear correlations became key means to assess trends in developments related to health matters; that is, slope-based rather than threshold analyses are employed largely here.[9,10]

2 Using FBG as a surrogate for the magnitude of IR, it is noted that those possessing a lower circulating FBG level, i.e., lower IR status, predominate in the surviving oldest elderly[9,10].

Baseline data were accumulated from male and female subjects (age 25–87 years). The material was collected from tests conducted from February 2014 to July 2019 on purportedly "nondiabetic, healthy subjects" who had agreed to participate after they received a Consent Form and were requested to review the form with their healthcare provider to confirm that they had no medical conditions that would preclude their involvement. Information was used only from subjects with a circulating FBG level in the nondiabetic range (125 mg/dL or less). Individual data employed for analyses were limited to values within three standard deviations of the group mean. This created very little elimination of material, and data from 1049 subjects were still left to evaluate material from volunteers who granted written permission to use the redacted data in future analyses. "Resting" blood pressures were obtained after study participants had remained prone for ~15 min while completing their DEXA testing. All study participants executed an informed consent form in compliance with the Helsinki Declaration and were allowed to participate by the independent Institutional Solutions Review Board (IRB) (http://ohrp.cit.nih.gov/search/IrbDtl.aspx). Quest diagnostics conducted all blood testing after study participants had fasted for at least ten hours. Quest also provided the glomerular filtration rate (GFR) readings estimated from circulating creatinine values.[31] These are listed as "eGFR." To measure the strength and direction of the relationship between correlations, the Pearson correlation coefficient ® was used to calculate the significance level (*P*).

Time intervals considered

The first period consists of the developmental stage, where individuals are growing from childhood and mature into adulthood. This time interval is devoted largely to growth and development, which was specified to last through the age of 24 years. The second period begins with the initiation of the characteristic decline in the renal GFR.[22] This mechanism (declining GFR) may be intrinsically related in some manner to the general aging phenomenon preceding final declining health and eventual death.[9,10] This life cycle aging period in the data interpretation presented arbitrarily begins at 25 years of age and lasts until 70 years. During this longest designated period of the arbitrary lifecycle, many risk factors pertaining to MetS and the aging process continue to progress. The functioning of a variety of risk factors such as blood pressure, a multitude of dyslipidemias, and glucose-insulin perturbations is taking place and providing a continuum of metabolic risks linked to the aging process despite not usually reaching levels consistent with any disease diagnoses – especially for our purpose, diabetes mellitus.

For a more precise approximation, the timing is sometimes split in the period that we have labeled in the past "Continuum of Risks" (CR).[9,10] This temporal interval is at times opportunely divided here further into an earlier (CR early, 25–50 years) period and a later (CR late, 51–70 years) period.

The 3rd time sequence (Aging Paradox [AP]) is set here to begin at 71 years and end at the oldest age level, 87 years.[9,10,14] This last temporal stage contains an unanticipated paradox that often defies reason when compared to the preceding CR period – marked improvements in many aspects of the glucose-insulin system relating to MetS.

RESULTS

Focusing on the association of declining human eGFR over the lifespan with the IR surrogate FBG and the level of systolic blood pressure (SBP)

Two major metabolic driving forces behind age-related GFR decline are circulating FBG levels, which can be used as a surrogate for the strength of IR, and secondarily, elevations of SBP.[18,20,22] Figure 1 displays the relationship between FBG and eGFR. A statistically significant negative correlation is revealed. Accordingly, when FBG rises, eGFR decreases. In contrast, when fat mass (FM) replaces FBG as the independent variable, no such statistically significant relationship is evident positively or negatively (R = 0.024778, n = 670, P = 0.522) (figure not shown). In Figure 2, the elevation in SBP is highly and significantly correlated with the decline of the eGFR over the combined CR period, as previously reported.[18]

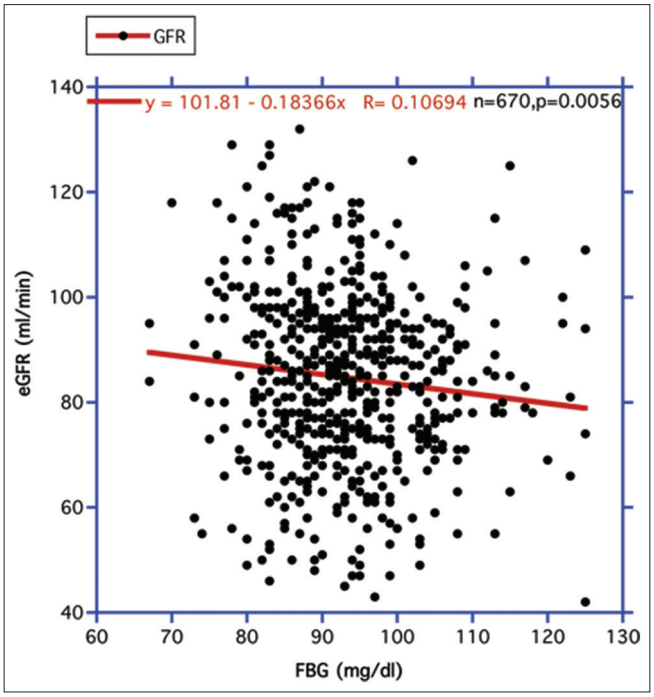

Figure 1: FBG, a surrogate for IR, versus eGFR. Despite the possibility of wide variations among the volunteers of different gender and stages in life over the continuum of risks period (ages 25–70 years), a statistically significant negative correlation is still found between the FBG as the independent variable and the eGFR as the dependent variable. A higher circulating FBG has been associated previously with a lower eGFR.[20] FBG: Fasting blood glucose, IR: Insulin resistance, eGFR: Estimated glomerular filtration rate.

Comparing the progression of eGFR and FBG over the arbitrary lifespan

Unlike previous findings,[21] we did not uncover an ever-increasing rate of eGFR descent in Figure 3 over the lifespan in the two consecutive CRs periods black dots/red line for early (25–50 years) and open dots/blue line for later (51–70 years) periods respectively. There seemed to be a lessening of the decline over the later temporal interim compared to the earlier CR period. In any case, there was no eventual increase in the rate of descent with age between these first two timed separations. During the period referred to as the AP (71–87) years portrayed here by the green diamonds orange broken line), the decline was even less. Unlike the preceding two

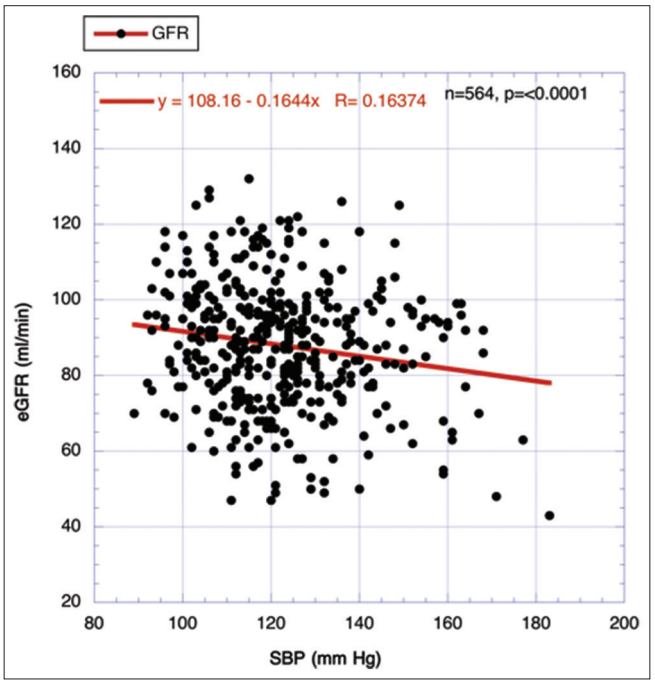

Figure 2: This depiction demonstrates the statistically significant correlation between SBP and eGFR in the early (25–50 years) and late (51–70 years) CR periods combined, i.e., during the whole CR period. A higher SBP has previously been associated with a lower eGFR during aging.[20] CR: Continuum of risks, SBP: Systolic blood pressure, eGFR: Estimated glomerular filtration rate.

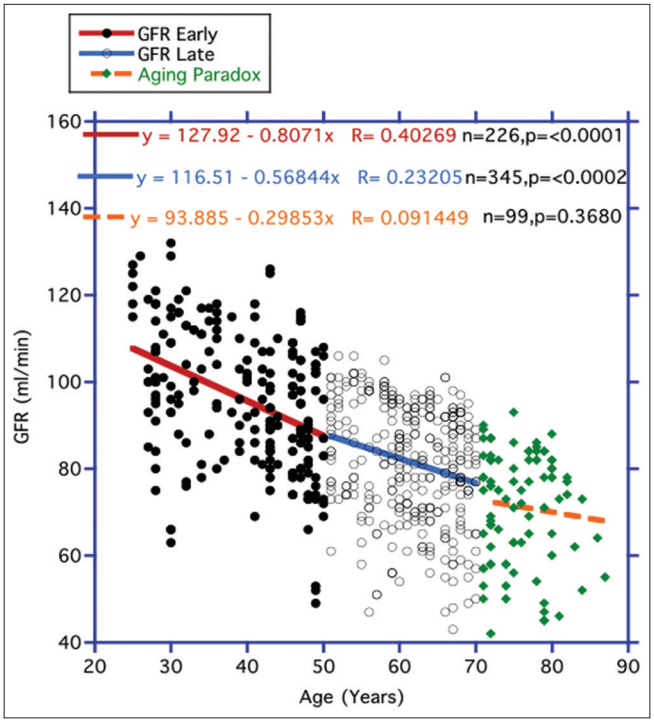

Figure 3: Age versus estimated glomerular filtration rate in this cross-sectional examination showing a gradual lessening in the descent rate during the continuum of risks time interval (early period 25–50 years represented by black dots and solid red line; and late period 51–70 years represented by open dots and solid blue line). Within the aging paradox period (71–91 years in this grouping represented by green diamonds and broken orange line), the negative linear regression line does not retain the statistically significant slope.[9,10]

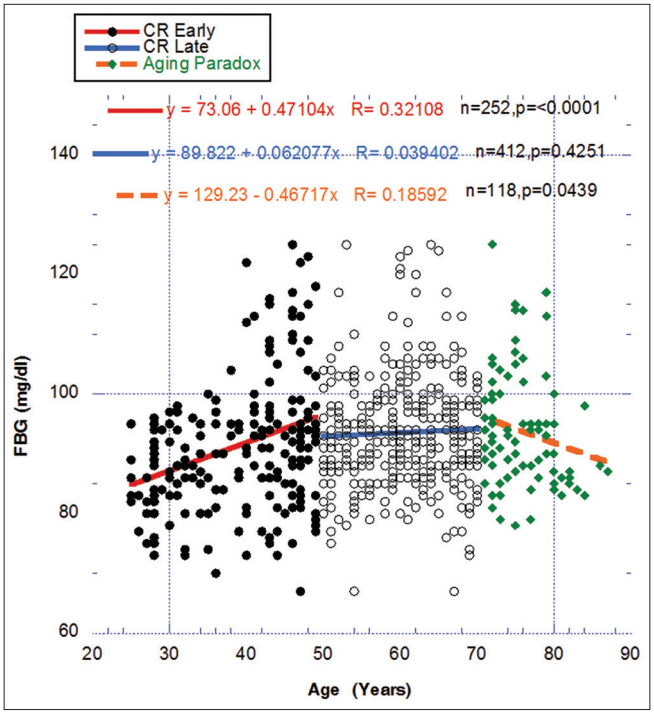

Figure 4: Cross-sectional examination of fasting blood glucose levels, used as a surrogate for IR, over the early CR period (black dots, solid red line), and the late CR period (open black dots, solid blue line) are portrayed. The early CR (25–50 years) shows a positive increase in slope that levels off somewhat in the late CR period (51–70 years). The aging paradox period (green diamonds, orange broken line) after age 71 years shows a significant negative slope.[9,10] IR: Insulin resistance, CR: Continuum of risks.

designated CR periods, a statistically significant negative correlation was not established for this temporal interval ($P = 0.3680$).

For comparative purposes with the previous figure, Figure 4 portrays a similar temporal relationship between FBG, a surrogate for IR, over the three designated periods between ages 25 and 87. Even with a more precise definition of the overall CR period, the early rise and eventual maintenance in FBG over the early and late CR periods coincides with the gradual reduction in eGFR in Figure 3. In contrast, the modification to a less significant descent of eGFR in the AP period Figure 3 matching the statistically significant changing negative direction of FBG also in the AP period Figure 4 strengthens the possibility of a meaningful relationship between IR and the declining eGFR. Does this represent in this figure an overall metabolic alteration, that is, improvement in healthful metabolism in the AP period compared to the CR period?

Figure 5 compares the separate correlations between the whole CRs period and the AP period using FBG as the independent variable and one selected aspect of the MetS cadre – alanine aminotransferase (ALT) as the dependent variable. The CR period shows significant upward mobility for ALT, while the AP period reveals a significant negative descent. The very close correlations in Figure 6 between the two CR and AP periods in ALT slopes suggest no real change in IR, and the hepatic enzyme activity relationships in those periods explain the occurrence of the paradox through changing major metabolic parameters. This strengthens the survivor bias theory considerably.

Corroboration through another surrogate for IR, that is, ratio of Tri/HDL-cholesterol, correlating with characteristic descent of eGFR during aging

The ratio between Tri and HDL-cholesterol has been used effectively as a surrogate for IR, and different investigators have previously found a strong relationship between the strength of IR and the ratio.[22-26] Data from 800 volunteers (ages 25–87 years), a highly statistically significant positive correlation, was found between FBG and the ratio Tri/HDL-cholesterol ($P < 0.0001$) [Figure 7].

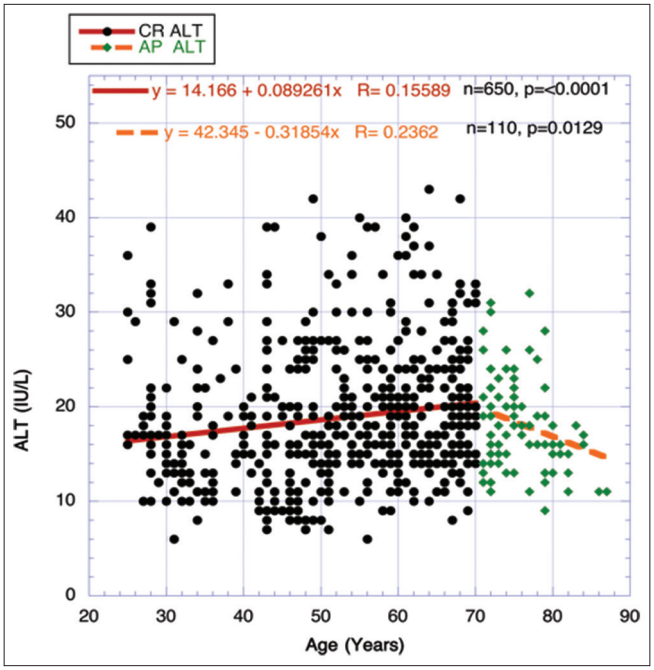

Figure 5: Comparing age-related changes in NAFLD represented by ALT levels in CR Period (black dots, solid red line) and aging paradox period (green diamonds, orange, broken line). The hepatic organ perturbation is now widely considered to be a valid component of MS.[9] ALT: Alanine aminotransferase, CR: Continuum of risks, NAFLD: Non-alcoholic fatty liver disease.

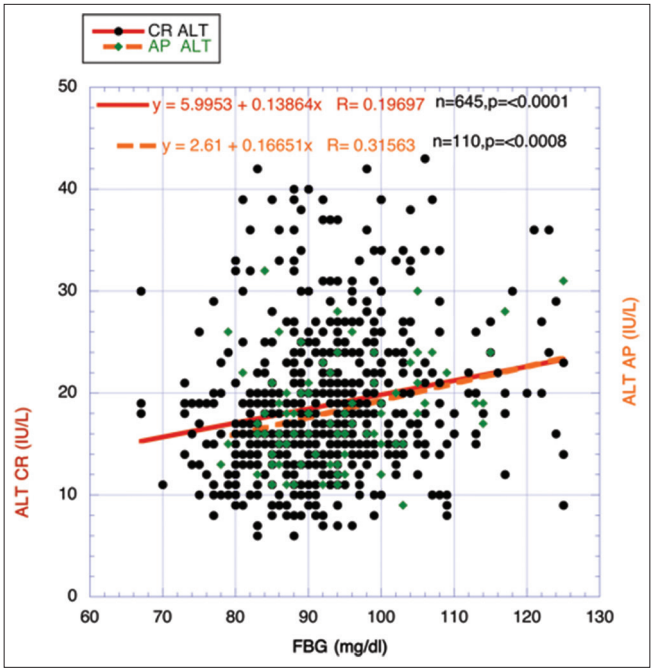

Figure 6: Fasting blood glucose versus ALT in overall CR period – black dots, solid red line, 25–70 years and aging paradox period – green diamonds, broken orange line, 71–91 years. The correlation lines from the two periods overlap and resemble, for the most part, a single line. No obvious changes in glucose-insulin metabolism between periods.[9] ALT: Alanine aminotransferase, CR: Continuum of risks.

In Figure 8, the independent variable FBG was replaced with the ratio Tri/HDL-cholesterol as a surrogate for IR. Over the entire CR period in Figure 8 (25–70 years), the strength of IR represented by the ratio increases significantly, but during the AP period (71–87 years), IR shows a significant downward decrease like that shown for FBG and ALT in Figures 4 and 5.

Figure 9 once more resembles the previous outcome for ALT in Figure 6; that is, no significant metabolic changes take place in the correlation slopes between FBG and Tri/HDL from the two temporal periods to account for any significant metabolic changes between these two independent variables during the CR and AP Periods.

Comparison of eGFR with various components of MetS

During the long CR period that comprises 46 years (ages 25–70 years), several statistically significant associations appear when correlating eGFR as the independent variable with various components of MetS [Table 1]. The slopes using the declining eGFR as the independent variable were significantly negative with passing time for FBG, SBP, low-density lipoprotein-cholesterol, Tri, non-HDL-cholesterol, and ALT.[3]

3 Considering the negative slope of the independent variable, the associated components actually increased with the declining eGFR.

FM and HDL-cholesterol revealed no statistically significant linkages. A previous suggestion has been strongly accepted that IR, represented here mainly by circulating FBG levels, not so much FM, drives most elements comprising MetS.[28]

DISCUSSION

Historical recognition of the insulin-resistant-driven MetS

Reaven, in the 1980s, emphasized the close connection between several adverse detrimental metabolic events such as corpulence, glucose-insulin aberrations, lipid abnormalities, and elevated blood pressure.[1,28] Even more exceptional, Reaven promoted the fundamental concept that intensified IR, a most prominent glucose-insulin abnormality, is the primary driving force behind the other accompanying harmful components of MetS. The associated metabolic interactions predominate in the elderly also proved to be valuable critical information, particularly regarding the current presentation.[1,11,28]

Ironically, the specific recognition of the perturbed glucose-insulin interplay (IR) as a major driving force behind other metabolic aberrations had not been generally recognized earlier on despite its evident importance then and now. This key perception, as pointed out by Morley and Sinclair, only

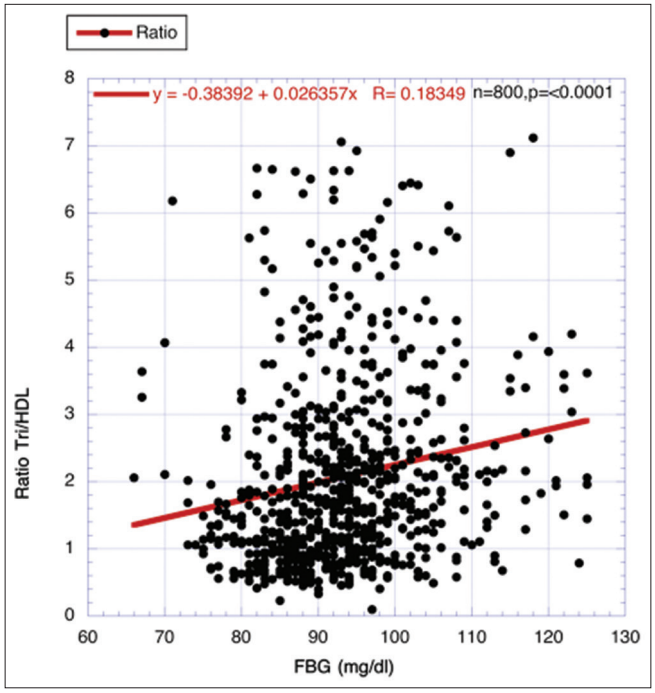

Figure 7: Depicting the correlation between fasting blood glucose and the ratio Triglyceride/HDL-cholesterol to strengthen the use of the ratio as a valid surrogate for IR strength.[25,26] HDL: High-density lipoprotein, IR: Insulin resistance.

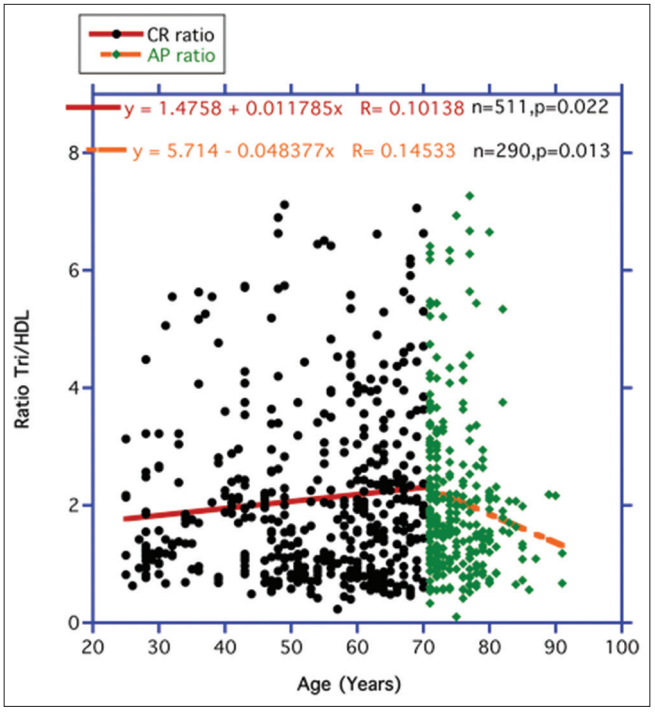

Figure 8: Effects of age in years during the entire CR and the AP periods are illustrated. Findings with the ratio simulate those when fasting blood glucose is utilized as the surrogate Figure 4, that is, once again, the significant positive slope for the new surrogate in the CR period (25–70 years, black dots, solid red line) is replaced by a statistically significant, negative one in the AP period (71–91 years, green diamonds, broken orange line).[25,26] CR: Continuum of risks, AP: Aging paradox.

blossomed at the beginning of the 1920s.[32,33] Conceivably, much confusion may have arisen based on nomenclature difficulties because this syndrome has had several differing labels over the years. The grouping of hyperinsulinemia, hypertriglyceridemia, and hypertension was initially promoted as "Syndrome X."[1] This metabolic collection was retitled "insulin resistance syndrome" to emphasize the importance of events that produce and amplify adverse health elements.[34] Nevertheless, a term attributed to Haller in 1977 predominates today, and the clustering and linking of the characteristic aspects, along with many new additions, are now universally established and recognized as the "Metabolic Syndrome."[35]

Defining the MetS

The generally accepted form of MetS comprises many familiar health risk factors that are solidly linked to the development of cardiovascular,[1,3,24,28,36,37] hepatic,[9,38-40] and renal infirmities.[41-46] The diagnosis of MetS is IR/T2DM; overweight/obesity; dyslipidemias (specifically hypertriglyceridemia and low HDL-cholesterol levels); and elevated SBP/hypertension readings.[1-3,47] The effect of MetS can include coagulation difficulties,[48,49] amplified general inflammation,[28,50] and/or fatty infiltration of the liver (Non-alcoholic fatty liver disease, NAFLD).[38-40] Indeed, the intertwined triad of MetS, T2DM, and NAFLD closely share many pathophysiologic characteristics.[40]

Informative background dealing with the role that IR and linked metabolic components have on healthy well-being and aging in nondiabetic individuals

A close correlation exists between IR and various metabolic risk factors found in our purported abated version of MetS.[51,52] Employment of circulating concentrations of FBG, insulin, and/or HbA1C as the independent variables representing IR in cross-sectional investigations shows strong links with various components of MetS when using correlative assessments.[32,33] It is essential to accentuate that the present material employed originated from relatively healthy volunteers (no conclusive evidence of diabetes) receiving baseline evaluations to eliminate actual diagnosed T2DM before entering a variety of clinical studies. In these volunteers, risk factors associated with MetS usually intensify gradually with time passage. Generally it is observed between chronological ages between 25 and 70 years.[9,10] As mentioned in the Methods Section, we labeled this temporal phase "Continuum of Risks," a period whereby the metabolic maladies that correlate with glucose-insulin perturbations usually adjust unfavorably but, for the most part, rarely exceed or fall outside ranges that would diagnose established

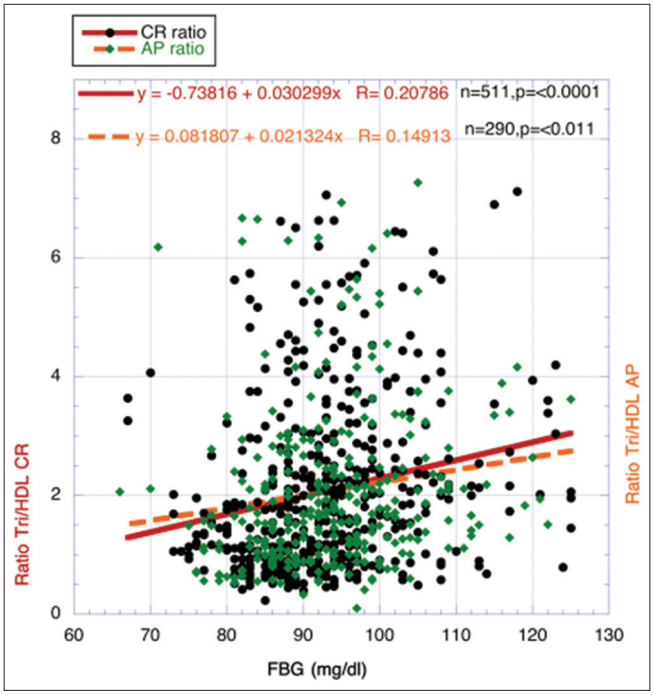

Figure 9: Correlation of slopes using fasting blood glucose as independent variable versus ratio triglycerides/HDL-cholesterol issuing from CR period (25–70 years, black dots, solid red line) and the aging paradox period (71–91 years, green diamonds, broken orange line).[25,26] CR: Continuum of risks, HDL: High-density lipoprotein.

Table 1: Correlating parameters linked to the metabolic syndrome throughout the active continuum of risks period with the declining eGFR in human volunteers.

Dependent variable	*N*	Slope	R	*P*
FBG (mg/dL)	571	−0.057	0.09464	**0.023722**
SBP (mmHg)	549	−0.130	0.13337	**0.001737**
Fat mass (pounds)	565	+0.041	0.02284	0.587978
Triglyceride (mg/dL)	578	−0.317	0.08692	**0.036696**
HDL-cholesterol (mg/dL)	564	−0.026	0.02638	0.531834
LDL-cholesterol	526	−0.280	0.14904	**0.000361**
Non-HDL-cholesterol	532	−0.306	0.14145	**0.001070**
ALT (IU/L)	567	−0.055	0.12816	**0.003401**

Independent variable is eGFR. *n*: number of observations considered. Bold denotes statistical significance ($P<0.05$), eGFR: Estimated glomerular filtration rate, FBG: Fasting blood glucose, SBP: Systolic blood pressure, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, ALT: Alanine aminotransferase

pathological diseases. Ironically, much further along the age scale in our cross-sectional analyses, the potencies of some of these risk factors surprisingly appear to revert significantly in an opposite, beneficial direction.[9,10,53]

Because separating and then comparing data from the CR and AP periods does not reveal any significant variances in the glucose-insulin relationships and their connection to other components of MetS, the favorable direction of experiences in AP is largely attributed to "Survivor Bias" rather than counteracting metabolic modifications.[9,14] The meaning behind this is that those volunteers possessing the more promising profile of risk factors over time can contribute actively to ongoing clinical studies, whereas participants with poorer profiles may not participate as volunteers in later life due to medical debilities or even death[4].

In solid corroboration with this interpretation, De Boer *et al.* have been able to show in one of their studies that older adults with the highest insulin sensitivity index (ISI) and/or circulating fasting insulin levels were the most prone to increased risk of death.[36] ISI was calculated from fasting and 2-h post-load insulin and glucose concentrations. Correspondingly, the level of FBG, our routine surrogate for IR in nondiabetic volunteers, has long been noted to be a risk factor for cardiovascular death.[37] Finally, data from a few studies dealing with centenarians confirm the importance of maintaining ideal glucose-insulin regulation in prolonging lifespan.[54-56] Healthwise, the average values of the following markers changed in a favorable direction from the CR period when evaluated in the later AP period in our volunteers: body weight, FM, and levels of FBG, Tri, and ALT enzyme.[14]

Providing substantiating confirmation is accomplished by two separate prominent changes in the protocol: first, by examining in detail a relatively fresh surrogate for IR, the ratio Tri/HDL cholesterol [23-26], and second, by comparing the effects of IR along with its "MetS risk factors" on the age-related decline in GFR, we believe to be a well-recognized model of age-related senescence.[21] These additional findings based on different markers would be compared with the former surrogates and CRs and Paradox periods in the original chronological aging studies[15-22] [Figures 3, 4, 9].

Newer surrogate for IR – Tri/HDL cholesterol ratio

IR primarily infers a less than adequate metabolic functioning of insulin, resulting in a poorer uptake of glucose by muscle and fat tissue as well as improper excess release of glucose by the liver.[57,58] The first novel adjustment in our protocol uses the ratio Tri/HDL cholesterol to replace FBG as the primary variable. The ratio should represent some peripheral inhibition of insulin action through the muscle and fat tissue as well as the hepatic release of glucose in its assessment. In contrast, FBG as a surrogate largely represents just the latter.[36,55] Despite these acknowledged differences, they both

4 Accordingly, a higher proportion of volunteers with the lower FBG levels would decrease the calculated average for that age level. Referring to an earlier publication describing the concept using material from a "caloric restriction rat study" might be helpful for clearer comprehension of the survivor bias theory[9]

accomplish the same purpose, appearing to be reasonable first approximations.

Declining GFR during characteristic aging

Regarding the second major adjustment in the protocol, a series of cross-sectional studies mixed in with a few longitudinal ones reveals that the renal GFR of humans characteristically declines in a gradual but steady manner over the lifespan.[15-21] While the precise direct cause(s) behind this phenomenon continue to remain somewhat unresolved, Davies and Shock were at least the first to demonstrate that GFR regresses with age in mature individuals apparently free of precise, perceptible cardiovascular disorders, renal diseases, and other acute illnesses except for high circulating glucose levels and blood pressure.[15,18] To further bolster this observation, the distribution of the decreasing age-related GFR slopes being Gaussian rather than bimodal suggested to Glassock and Winearls that the steady waning GFR process(es) involved is (are) "involutional" by nature – not resulting from recognizable, recurring, disease causation.[21]

IR can be reasonably correlated with the characteristic age-related decline in the renal eGFR before reaching specified threshold levels necessary to diagnose defined pathologic entities

Two irrefutable findings have been established beyond reproach – one relating to "pathology" and the second embodying "normality." Regarding the first pathological discovery, serious glucose-insulin perturbations in MetS (heightened IR and/or diagnosed T2DM) along with their associated, linked entities have long been connected to renal pathology affecting GFR, that is, elevated blood glucose plus insulin, along with SBP values[4,15,17,18,20,42-45,59] [Figures 1 and 2]. Dealing with the second finding regarding acknowledged normality, a gradual but persistent decline in GFR takes place over the usual, natural human life cycle despite a lack of blatant pathologic interference.[21,45] Nevertheless, we have linked the latter, at least in part, to a "slight but significant escalation" of IR, even though most interested parties might presently prefer the term "innocuous."[22] Hence, the question directly addressed in this report relates to the precise involvement between these two established pathological and natural happenings.

There is considerable acknowledgment that IR linked to less-than-optimal lifestyle choices may be the most important pathological driving force behind MetS.[1-3,28] Based on this relatively solid assumption, the finding that MetS coincides with the expected age-related decline in eGFR, a substantial negative correlation between the rising levels of circulating FBG as the surrogate for estimating the intensity of IR and eGFR might not create any surprise [Figure 1]. In contrast, the age-related, declining eGFR cannot be conclusively linked to accumulated FM here.[22] In support of the preceding, Reaven previously emphasized that IR influences the cardiovascular and renal systems in MetS to a much greater extent than obesity, adding further corroboration to the material in Table 1.[28]

The closeness of timing changes regarding shifting higher levels of circulating FBG that influence insulin sensitivity along with the declining GFR in the early and late CRs and AP periods displayed in [Figures 3 and 4] also bolster the proposition that IR possesses some distinct control over the age-related declination of eGFR. To be more precise, the decline in renal function begins somewhere around the chronological age of 25–30 years – a temporal point that coincides with the development of rising FBG levels and SBP values.[22] The ascent in FBG level is of paramount importance since changes in its circulating concentrations reflect the strength of IR.[52,53] Finding a variety of similar temporal relationships when the ratio Tri/HDL cholesterol replaces FBG levels as IR surrogates also supports a cause and effect between eGFR and sensitivity to insulin [Figures 3, 4, and 8].

The correlative nature of the descending eGFR with multiple ascending components of MetS, as portrayed in Table 1, is further reassurance. In the face of declining eGFR, increases in FBG, SBP, LDL-cholesterol, non-HDL-cholesterol, and ALT are noted in Table 1, along with essentially no changes when correlating with body FM (n = 666, r = +0.0008, P = 0.984). Wing *et al*. showed convincingly that caloric restriction in humans rather than the magnitude of weight loss plays a more important role in the improvement of glycemic control and insulin sensitivity.[27] Why? Perhaps because an increase in caloric intake from both carbohydrate and fat consumption no doubt brings about more overweight/obesity, but the IR is produced primarily from the accompanying raised sugar and refined carbohydrate intakes that occur with the increased food load. The data described here should encourage the use of optimal lifestyle choices to maintain good health and encourage longevity, keeping the following in mind.

Starting on such ideal regimens ought to begin early in life, that is, in the 20s following the general maturation period (<25 Years). Knowing that it is difficult to consistently maintain the best lifestyle regimen (Diet and Exercise) in today's world with all the temptations about – additionally taking safe, effective, daily dietary supplements and/or proven, safe drugs that enhance insulin sensitivity and overcome IR should be considered. In the supplement realm to allay abated MetS, we have had some positive experiences with trivalent chromium,[60] cinnamon,[61] Maitake SX mushroom preparation,[62,63] and vitamin D3.[64] The latter has been used in an attempt to lessen much of the distress created by COVID-19, as the infections seem to worsen in the presence of MetS risk factors.[65] Keeping the body in optimum shape by reducing IR throughout aging may help mitigate all sorts

of infectious processes occurring in one's lifetime.[65] In the drug realm, much information has come forth on the use of metformin to enhance longevity in animals basically through its beneficial effects on insulin metabolism.[66-71]

CONCLUSION

Ultimately, the objective is to maintain the body in optimal shape by reducing IR throughout aging. This may help mitigate all sorts of metabolic disorders, including infectious processes occurring in one's lifetime.

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