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Four-Stage Evolution of Diabetes or Whole-Body Insulin Resistance (WBIR): Debunking of The Lipid-Induced Insulin Resistance (LIIR) and Proposing of the Glycation-Induced Insulin Resistance (GIIR)

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Abstract

Insulin resistance (IR) would develop first preferentially in the muscle tissue with a relatively low cell turnover and then progress in sequence to the subcutaneous adipose tissue, then to the visceral adipose tissue, and then to the liver with higher cell turnovers. Moreover, metabolic disruptions due to IR would vary widely from tissue to tissue, contrary to the widespread notion that IR impairs merely glucose uptake in tissues. This warrants that IR be divided better into four distinct tissue-specific IRs: muscle insulin resistance (MIR), subcutaneous adipose insulin resistance (s-AIR), visceral adipose insulin resistance (v-AIR), and hepatic insulin resistance (HIR). Tissue-specific IRs developing in the order of MIR, s-AIR, v-AIR, and HIR with uniquely tissue-specific metabolic disruptions would amount to nothing but the whole-body insulin resistance (WBIR) evolving in four distinctively insulin-resistant stages, IR-I to IR-IV stage. The four-staged metabolic evolution from rapid weight gain (IR-I stage) to visceral obesity (IR-II stage), then to rapid weight loss (IR-III stage), and then to full-blown diabetes (IR-IV stage) not only complies well with the natural development history of diabetes but also resolves many controversies regarding obesity or diabetes, including visceral obesity, obesity paradox, and dawn phenomenon that have long remained metabolic puzzles. In addition, the entrenched notion of the lipid-induced insulin resistance (LIIR), which is refuted by four-stage WBIR evolution and believed to be the main culprit for the current epidemic of obesity and diabetes around the world, was debunked thoroughly. Then, in order to replace the LIIR, the glycation-induced insulin resistance (GIIR) was proposed and verified to be compatible to the four-stage WBIR evolution.

Keywords: Obesity, Obesity Paradox, Diabetes, Insulin Resistance (IR), Whole-Body Insulin Resistance (WBIR), Tissue-Specific Insulin Resistance, Muscle Insulin Resistance (MIR), Subcutaneous Adipose Insulin Resistance (s-AIR), Visceral Adipose Insulin Resistance (v-AIR), Hepatic Insulin Resistance (HIR), Lipid-Induced Insulin Resistance (LIIR), Glycation-Induced Insulin Resistance (GIIR), Metabolic Syndrome.

1. Introduction

Insulin resistance (IR) plays a central role in the development of (type 2) diabetes, which appears to be at the center of association among many disorders, such as cardio/cerebral vasculopathy, nephropathy, neuropathy, and retinopathy. IR may be defined as the physiological state or condition, in which cells or tissues have been deranged enough so as to be unable to respond properly to insulin, the major hormone regulating the energy metabolism. Conventionally, IR has been considered to merely impair glucose uptake in tissues. Given that, however, the role of insulin is very different from tissue to tissue, metabolic disruptions due to IR would be very tissue-specifically wide-ranging [1-4].

No less importantly, IR would not necessarily develop simultaneously over the whole body. In principle, it would be more likely to develop first preferentially in old cells over newly formed cells, simply because old ones would have been exposed longer to potential IR-inducing agents than new ones – an important goal in this study is, in fact, to identify the IR-inducing agents or mechanisms. The lower the cell turnover in a tissue, the larger the population of old cells. Consequently, tissues with lower cell turnovers would develop IR earlier than those with higher cell turnovers.

Adipose tissues are unique in that they differentiate preadipocytes into adult adipocytes with energy storage demand increasing – adipogenesis. In contrast, myogenesis in muscle tissues appears to be much smaller than adipogenesis [5, 6]. This implies that the average cells in muscle tissues would be much older than those in adipose tissues, which translates into that muscle tissues would develop IR earlier than adipose tissues. Meanwhile, adipogenesis in the visceral adipose tissue is known to be much more active than that in the subcutaneous adipose tissue, which translates into that the subcutaneous adipose tissue would develop IR earlier than the visceral adipose tissue. In the case of the liver that serves also as the body's major chemical factory,

the cells would be more likely to be damaged and replaced rather frequently, giving rise to a very high cell turnover [7].

Based on this reasoning, we postulate that IR develop first preferentially in the muscle tissue and then progress in sequence to the subcutaneous adipose tissue, then to the visceral adipose tissue, and then to the liver. A noteworthy point here is that this postulation is contrary to the widespread notion that IR is a global parameter affecting the whole body simultaneously.

If IR indeed develop sequentially among various tissues, it would better be subdivided into tissue-specific IRs: muscle insulin resistance (MIR), subcutaneous adipose insulin resistance (s-AIR), visceral adipose insulin resistance (v-AIR), and hepatic insulin resistance (HIR). Sequential development of tissue-specific IRs in the order of MIR, s-AIR, v-AIR and HIR, as depicted in Fig 1, would amount to nothing but the whole-body insulin resistance (WBIR) evolving in four distinctively insulin-resistant (IR) stages, denoted by IR-I, IR-II, IR-III, IR-IV, respectively [8].

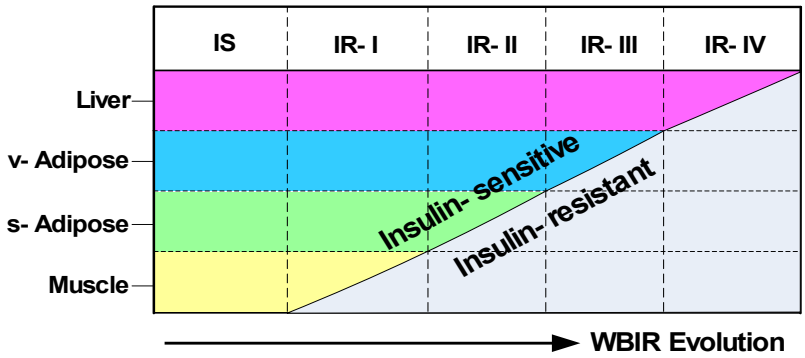

Figure 1: WBIR evolves in four distinctive stages as the tissue specific IRs develop in the order of MIR, s-AIR, v-AIR, and HIR. WBIR evolution would eventually lead to development of full-blown diabetes in the IR-IV stage, in which glucose uptake is impaired in the whole body and consequently the plasma glucose (PG) is elevated severely enough to be diagnosed of diabetes. In this sense, the four-stage WBIR evolution would, in reality, amount to the four-stagee diabetes evolution.

2. Design of the Study and the Methodology

The aim of this study is to develop a comprehensive diabetes evolution model that complies well with the natural development history of diabetes [9]. We postulated that IR develop first in the muscle tissue and then progress in sequence to the subcutaneous adipose tissue, to the visceral adipose tissue, and to the liver. A proposition that follows naturally from this postulation is that WBIR would evolve in four distinctively insulin-resistant stages. The four-stage WBIR evolution model was then validated based on integrated approach we described in detail elsewhere [10]. By adopting the integrated approach, we barely need to conduct any experiments of our own simply because we can readily exploit virtually unlimited amounts of experimental results available from literatures of wide range of disciplines. Importantly, all the literature review in this study was done only either to support the WBIR evolution model or to debunk the notions that are hardly compatible to the model. In this sense, our research is very much original.

3. Tissue-Specific IRs

Metabolic disturbances due to tissue-specific IRs may easily be deduced by studying the tissue specific roles of insulin and then largely verified by comparing with the those observed in some genetically engineered tissue-specific IR models, like MIRKO (muscle-tissue specific insulin receptor knock out), FIRKO (fat-tissue specific insulin receptor knock out), and LIRKO (liver-specific insulin receptor knock out) mice [2-4]. Obviously, the MIRKO, FIRKO, and LIRKO mice would be unable to initiate insulin signaling in the muscle tissue, adipose tissue, and liver, respectively, and therefore exhibit MIR, AIR, and HIR, respectively. Key aspects of tissue-specific IRs are summarized in Table 1. Importantly, aspects of IR vary widely from tissue to tissue, which refutes the common belief that IR impairs merely glucose uptake in the whole body.

MIR	● Disruption of insulin signaling in the muscle tissue ● Impairment of insulin mediated muscle glucose uptake and muscle glycogenesis ** PPG elevated significantly ** PI (PPI and FPI) elevated significantly (as long as insulin secretory response is still intact) ● However, muscle glucose uptake mediated by muscle contraction or exercise is largely spared from MIR
s-AIR	● Disruption of insulin signaling in the subcutaneous adipose tissue ● Impairment of the subcutaneous adipose glucose uptake: ** PPG elevated significantly ** PI (PPI and FPI) elevated significantly (as long as insulin secretory response is still intact) ● Impairment of s-ADNL and subcutaneous fat accumulation in the fed state ● Subcutaneous adipose tissue undergoes uninhibited lipolysis and fails to entrap the FAs released from TRLs ** Subcutaneous adipose tissue losing fat mass rapidly

v-AIR	● Disruption of insulin signaling in the visceral adipose tissue ● Impairment of visceral adipose glucose uptake: ** PPG elevated significantly ** PI (PPI and FPI) elevated significantly (as long as insulin secretory response is still intact) ● Impairment of v-ADNL and visceral fat accumulation in the fed state ● Visceral adipose tissue undergoes uninhibited lipolysis and fails to entrap the FAs released from TRLs ** Visceral adipose tissue losing fat mass rapidly
HIR	● Disruption of insulin signaling in the liver ● Impairment of hepatic glucose uptake and hepatic glycogenesis: ** PPG elevated significantly ** PI (PPI and FPI) elevated significantly (only if insulin secretory response is still intact) ● Impairment of HDNL and VLDL generation in the fed state ● Liver undergoing unsuppressed HGP: ** PPG elevated even more ** FPG elevated severely as well: fasting hyperglycemia

Table 1: Key aspects of tissue specific IRs.

3.1. Muscle Insulin Resistance (MIR)

MIR or disruption of insulin signaling in muscle tissues as observed in the MIRKO mice would impair muscle glucose uptake, thereby significantly restricting muscle glucose oxidation as well as muscle glycogenesis [2]. Consequently, postprandial plasma glucose (PPG) would be elevated significantly, which would in turn enhance postprandial insulin secretion significantly thereby elevating significantly the postprandial plasma insulin (PPI).

It is quite unusual, however, that the hyperglycemia observed in the MIR exhibiting MIRKO mice is relatively mild, especially considering that muscle tissues are known to be responsible for more than about 70 % of glucose disposal in the whole body. This may serve as a strong evidence that muscle tissues have other glucose uptake pathway that is mediated, independently of insulin, by muscle contraction or exercise and thus largely spared from MIR [11-13].

3.2. Adipose Insulin Resistance (AIR)

AIR or disruption of insulin signaling in adipose tissues as observed in the FIRKO mice would not only impair adipose glucose uptake – thereby elevating PPG and PPI significantly – but also disrupt the adipose metabolism seriously. In order to understand properly how AIR disrupts adipose metabolism, it would be essential to understand first the healthy adipose metabolism [4].

In the case of the fed state regulated by significantly elevated PPI and PPG, healthy adipose tissues would actively take up the glucose from the plasma and then mostly convert – via adipose de novo lipogenesis (ADNL) pathway – into fatty acids (FAs) [14, 15]. The amount of glucose oxidized to produce energy in the adipose tissues, which are specilaized for storing energy, would usually be minimal compared to that oxidized in the muscle tissues, which usually needs a great amount of energy for doing mechanical work. Healthy adipose tissues in the fed state would also entrap the FAs released – with the help of lipoprotein lipase (LPL) – from triglyceride rich lipoproteins (TRLs), such as very low density lipoproteins (VLDLs) and chylomicrons [16]. The FAs either synthesized inside or fluxed from the plasma in the fed state would be mostly esterified, with the help of elevated PI, into fats for storage.

In the case of the fasted state regulated by relatively low fasting plasma insulin (FPI), adipose lipases, such as hormone sensitive lipase (HSL) and adipose triglyceride lipase (ATGL), would not be inhibited as strongly as in the fed state [17]. Consequently, healthy adipose tissues would undergo lipolysis and then release the resultant FAs into the plasma, thereby elevating the fasting plasma fatty acid (FPFA) significantly. The FPFAs abundant in the plasma would diffuse into other tissues or organs and subsequently be oxidized to produce energy [18, 19]. The healthy adipose tissues that actively accumulate fat in the fed state and then undergo lipolysis in the fed state to release FAs into the plasma may better be regarded not merely as a fat storage depot but as a kind of a fatty acid (FA) reservoir.

3.3. Adipose Metabolism Disrupted by AIR

As expected, however, AIR or disruption of adipose insulin signaling would prevent the adipose tissues from working properly as a FA reservoir. In more detail, insulin would no longer be able to inhibit adipose lipases strongly enough. Thus, the adipose tissues affected by AIR would not only undergo uninhibited lipolysis but also fail to entrap the FAs released from TRLs. Consequently, plasma fatty acid (PFA) would be elevated severely in the fed state as well as in the fasted state. The excess FAs either shunned by or additionally released from the AIR affected adipose tissues would easily diffuse into other tissues or organs, notably muscle tissues and liver, a fraction of which would subsequently be esterified into ectopic fats [20]. A revealing observation is that the A-ZIP/F-1 transgenic mice, which are genetically engineered to lack white adipose tissues to work as a FA reservoir, also exhibit significant amounts of ectopic fats, exactly like the FIRKO mice [21].

3.4. Elevated PFA Effectively Elevating PG

In principle, PG and PFA would compete with each other to be used as the substrate for oxidation – Randle cycle or glucose-FA cycle [22, 23]. This means that the severe elevation of PFA due

to AIR would inevitably elevate PG severely as well. A noteworthy point is that PG appears to be inherently at a significant disadvantage in competing with PFAs. In more detail, glucose molecule is polar or hydrophilic and therefore its transport across the plasma membrane of hydrophobic lipid bilayer would require not only insulin mediation but also special plasma membrane transporters, like GLUT4 and GLUT2 [24]. By contrast, FAs that are nonpolar or hydrophobic would diffuse rather freely across the plasma membrane [18,19,24]. This may explain why PFA is preferentially utilized over PG in diabetics, in which both PG and PFA are elevated severely. The reasoning that AIR inevitably elevates PG as well as PFA suggests conversely that healthy AIR-free adipose tissues also play essential roles in glucose homeostasis [25, 26].

3.5. AIR Depleting Fat Mass in Adipose Tissues

Another important point is that the AIR-associated uninhibited adipose lipolysis would inevitably lead to rapid depletion of the adipose fat mass or rapid weight loss. Conversely, this suggests only healthy, AIR-free adipose tissues are able to support weight gaining or obesity. This in turn suggests that weight gaining or obesity is an indication that at least one or both of the visceral and subcutaneous adipose tissue are working efficiently as a FA reservoir. In this sense, it would hardly be surprising that treatment of diabetes by anti-diabetic medications (ADMs), such as insulin or oral hypoglycemic agents (OHAs), often leads to weight gaining [27].

A noteworthy point in the Table 1 is that AIR is subdivided into the subcutaneous adipose insulin resistance (s-AIR) and visceral adipose insulin resistance (v-AIR), simply because we have postulated that the subcutaneous adipose tissue develop AIR earlier than the visceral adipose tissue.

3.6. Hepatic Insulin Resistance (HIR)

HIR or disruption of hepatic insulin signaling as observed in the LIRKO mice would not only impair hepatic glucose uptake – thereby elevating PPG and, as long as pancreatic insulin secretary response is still intact, PPI as well significantly – but also disrupt the hepatic metabolism seriously. Most importantly, insulin would fail not only to promote both the hepatic glycogenesis and the hepatic de novo lipogenesis (HDNL) but also to suppress hepatic glucose production (HGP). The unsuppressed HGP, regardless of PI level, would elevate PG in the fasted state as well as in fed state [3, 28]. In this sense, fasting hyperglycemia may be considered a hallmark of HIR.

An evidence that HIR indeed causes fasting hyperglycemia may be found in the so called dawn phenomenon regularly observed in diabetics treated by ADMs [29]. In diabetics undergoing treatment by ADMs, the PI would wane gradually overnight, which lets HGP be enhanced steadily until the next administration of ADMs usually early in the morning. On the other hand, exercise mediated glucose uptake into skeletal muscles would usually be minimal during sleep or rest. The combination of the maximal HGP and minimal exercise mediated skeletal muscle glucose uptake in the early morning hours would inevitably lead to severe elevation of PG – dawn phenomenon [30].

4. Four-Stage WBIR Evolution and its Validation

As schematically depicted in Fig 1, WBIB evolves in four distinctively insulin resistant stages denoted by IR-I, IR-II, IR-III, and IR-IV, respectively, as tissue specific IRs develop in the order of MIR, s-AIR, v-AIR, and HIR. The net metabolism observed in each stage can be estimated by cumulatively adding up – as by referring to the Table 1 – all the metabolic disturbances resulting from the tissue specific IRs developed thus far in that particular stage. Table 2 summarizes some important aspects of the metabolic disturbances to be observed in each stage.

IS	● Glucose uptake not impaired in the whole body ● PPG elevated only modestly with regular postprandial glycemic load ● Postprandial pancreatic insulin secretion modest: ** Relatively low PPI and FPI ** s-ADNL, v-ADNL, and HDNL activated only modestly in the fed state ** s-lipolysiss, v-lipolysis, and HGP inhibited only modestly in the fasted state ● FPFA and FPG (fasting energy substrates) relatively high: ** Intense physical activity accommodated relatively easily ** Feeling of hunger modest in the fasted state, rarely leading to overeating ● Rarely overweight or obese
IR-I	● Glucose uptake into the muscle tissue impaired: ** Excess PG diverted to the subcutaneous and visceral adipose tissues and liver ● PPG, PPI, and FPI elevated more than in the IS stage: ** s-ADNL, v-ADNL, and HDNL enhanced more than in the IS stage ** HGP suppressed more than in the IS stage ** s-lipolysis and v-lipolysis inhibited more than in the IS stage ● FPFA and FPG (fasting energy substrates) lower than in the IS stage: ** Intense physical activity accommodated rarely ** Feeling of hunger acute in the fasted state, likely leading to overeating ● Gaining weight rapidly: ** Both the subcutaneous and visceral adipose tissue increasing fat mass rapidly

IR-II	● Glucose uptake into the muscle tissue and subcutaneous adipose tissue impaired: ** Excess PG diverted to the visceral adipose tissue and liver ● PPG, PPI, and FPI elevated more than in the IR-I stage: ** v-ADNL and HDNL enhanced more than in the IR I stage ** HGP suppressed more than in the IR I stage ** s-lipolysis starting to be uninhibited ** v-lipolysis inhibited more than in the IR-I stage ** FPG lower than in the IR-I stage ** FPFA starting to rise gradually ● Visceral obesity: ** Subcutaneous adipose tissue starting to lose fat mass ** Visceral adipose tissue increasing fat mass more rapidly
IR-III	● Glucose uptake into the muscle tissue, subcutaneous and visceral adipose tissue impaired: ** Excess PG diverted to the liver ● PPG elevated more than in the IR-II stage: ** Pancreatic insulin secretory response possibly starting to be impaired near the end of this stage ** HDNL enhanced more than in the IR-II stage ** HGP suppressed more than in the IR-II stage ** s-lipolysis uninhibited more than in the IR-II stage ** v-lipolysis starting to be inhibited ** FPFA elevated severely ** FPG elevated significantly as well (glucose-FA cycle: elevated PFA restricts PG utilization) ** Ectopic fat deposition enhanced in the muscle tissue and liver ● Starting to lose weight rapidly: ● Likely to be diagnosed of diabetes near the end of this stage
IR-IV	● Glucose uptake into the muscle tissue, visceral and subcutaneous adipose tissue, and liver impaired ● PPG elevated more than in the IR-III stage ● Pancreatic insulin secretory response impaired severely: ** PPI and FPI dropped severely ● HGP unsuppressed: ** FPG as well as PPG elevated severely ● s lipolysis and v lipolysis uninhibited, but not sustainable with the fat mass largely depleted ** FPFA starting to drop below PPFA ** Weight loss no longer sustained ● Full-blown diabetes: ** Dawn phenomenon, when treated with ADMs

Table 2: Important aspects of metabolic disturbances to be observed in each of WBIR evolution stages

With WBIR evolving, various metabolic variables would also evolve in their own unique patterns. Table 3 describes how some important metabolic variables would evolve with WBIR evolving.

Stages	IS	IR-I	IR-II	IR-III	IR-IV
IRs developed	None	MIR	MIR, s-AIR	MIR, s-AIR, v-AIR	MIR, s-AIR, v-AIR, HIR
PPG	PPG_o	Rises steadily		Rises steeply	Rises more steeply
Insulin Sec.	Moderate	Increases steadily		Saturates then decreases	
PPI	PPI_o	Rises steadily		Saturates then declines	
FPI	FPI_o	Rises steadily		Saturates then declines	
s-ADNL	Moderate	Increases	Decreases gradually		
v-ADNL	Moderate	Increases steadily		Decreases gradually	
PPFA	$PPFA_o$	Declines	Rises modestly	Rises steeply	
HDNL	Moderate	Increases steadily			Decrease gradually
FPTG	$FPTG_o$	Rises steadily		Rises steeply	Saturates gradually
HGP	Moderate	Decreases gradually			Increases steeply

FPG	FPG_o	Declines gradually		Rises gradually	Rises steeply
HbA1c	$HbA1c_o$	Rises steadily		Rises steeply	Rises more steeply
s-Lipolysis	Moderate	Decreases	Increases	Saturates	Decreases gradually
v-Lipolysis	Moderate	Decreases		Increases	Saturates then decreases
FPFA	$FPFA_o$	Declines	Rises modestly	Rises steeply	Saturates then declines
Body Weight	Healthy lean	Increases rapidly	Saturates slowly	Decreases rapidly	Decreases slowly
Diabetes	Nondiabetic	Prediabetic			Diabetic

Table 3: General trend of WBIR dependent variation of some important metabolic variables.

The postprandial plasma glucose (PPG) rises steadily, until the visceral adipose tissue as well as the subcutaneous adipose develops AIR in the IR-III stage and undergoes uninhibited lipolysis elevating plasma fatty acid (PFA) severely and thereby restricting plasma glucose (PG) utilization severely, and therefore it rises steeply thereafter, until the liver develops HIR in the IR-IV stage undergoing unsuppressed hepatic glucose production (HGP), and therefore it rises even more steeply thereafter; The postprandial plasma insulin (PPI) rises steadily, until pancreatic insulin secretion possibly starts to be impaired at near the end of IR-III stage, and therefore it saturates and then decreases gradually thereafter; The fasting plasma insulin (FPI) behaves similarly as PPI, but with a level attenuated significantly from that of PPI; The subcutaneous adipose de novo lipogenesis (s-ADNL) increases steadily, until the subcutaneous adipose tissue develops AIR in the IR-II stage, and therefore it decreases gradually thereafter;

The visceral adipose de novo lipogenesis (v-ADNL) increases steadily, until the visceral adipose tissue develops AIR in the IR-III stage, and therefore it decreases gradually thereafter; The postprandial plasma fatty acid (PPFA) declines, until the subcutaneous adipose tissue develops AIR in the IR-II stage undergoing uninhibited lipolysis, and therefore it rises modestly thereafter, until the visceral adipose tissue also develops AIR in the IR-III stage undergoing uninhibited lipolysis, and therefore it rises steeply thereafter; The hepatic adipose de novo lipogenesis (HDNL) increases steadily, until the liver develops HIR in the IR-IV stage, and therefore it decreases gradually thereafter; The fasting plasma triglyceride (FPTG) rises steadily, until the visceral adipose tissue, in addition to the subcutaneous adipose tissue, develops AIR in the IR-III stage and fails to entrap PFAs thereby hampering VLDL delipidation, and therefore it rises steeply thereafter, until the liver develops HIR in the IR-IV stage thereby decreasing HDNL and VLDL generation and therefore it starts to saturate thereafter; The HGP decreases gradually, until the liver develops HIR in the IR-IV stage, and therefore it increases steeply thereafter; The FPG declines gradually, until the visceral adipose tissue, in addition to the subcutaneous adipose tissue, develops AIR in the IR-III stage undergoing uninhibited lipolysis elevating PFA severely and thereby restricting PG utilization severely, and therefore it rises gradually thereafter, until the liver undergoes unsuppressed HGP in the IR-IV stage, and therefore it rises steeply thereafter; The HbA1c level rises steadily, until the visceral adipose tissue as well as the subcutaneous adipose tissue develops AIR in the IR-III stage and undergoes uninhibited lipolysis elevating PFA severely and thereby restricting PG utilization severely, and therefore it rises steeply thereafter, until the liver develops HIR in the IR-IV stage undergoing unsuppressed HGP, and therefore it rises even more steeply thereafter; The s-lipolysis decreases gradually, until the subcutaneous adipose tissue develops s-AIR in the IR-II stage, and therefore it increases gradually thereafter, until the subcutaneous fat mass is largely depleted, and therefore it saturates then decreases thereafter; The v-lipolysis decreases gradually, until the visceral adipose tissue develops AIR in the IR-III stage, and therefore it increases gradually thereafter, until the visceral fat mass is largely depleted, and therefore it saturates and then decreases thereafter; The FPFA declines gradually, until the subcutaneous adipose tissue develops AIR in the IR-II stage undergoing inhibited lipolysis, and therefore it rises modestly thereafter, until even the visceral adipose develops AIR in the IR-III stage undergoing inhibited lipolysis, and therefore it increases steeply thereafter, until the visceral adipose fat mass is also largely depleted, and therefore it saturates and then decreases thereafter; The body weight increases rapidly in the IR-I stage, and then saturates slowly in the IR-II stage, and then decreases rapidly in the IR III stage, and then decrease slowly in the IR-IV stage; Lastly, typical values for PPG, PPI, FPI, PPFA, FPTG, FPG, HbA1c, and FPFA in the IS stage may be referred to as reference values and denoted by PPG_O , PPI_O , FPI_O, $PPFA_O$, $FPTG_O$, FPG_O , $HbA1c_o$, and $FPFA_O$, respectively.

4.1. Heuristically Drawn Metabolic Profiles

Actual measurement of WBIR dependent evolution of metabolic variables would be extremely difficult, simply because WBIR evolution would generally proceed very slowly over years or even decades. Moreover, detailed aspects of WBIR evolution would vary widely among individuals. Thus, WBIR dependent metabolic evolution profiles may better be drawn heuristically, for instance, by following the descriptions in Table 3. Important among them are the evolution profiles for PI, body weight, PFA, and PG, as depicted in Fig 2. It is noted that heuristically drawn, rule of thumb profiles would be good enough as long as they provide general idea of how metabolic variables vary from one stage to the next stage.

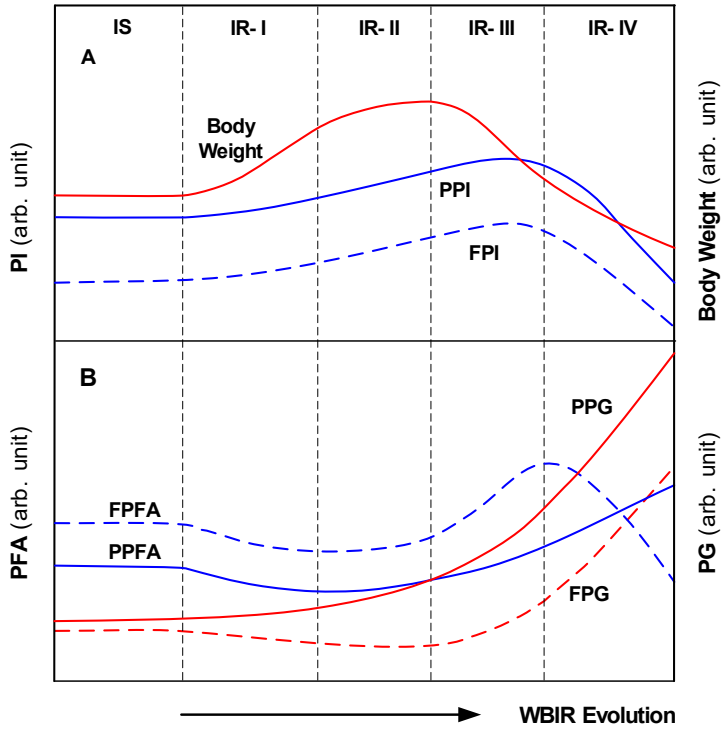

Figure 2: Heuristically drawn WBIR dependent evolution profiles for PI and body weight (A), and for PG and PFA (B)

Insulin is the major hormone that regulates the energy metabolism. This means that the most important determinant of the metabolism would be none other than PI. As long as pancreatic insulin secretory response is largely intact as in the early stages of WBIR evolution, postprandial insulin secretion would rise proportionally to the postprandial plasma glucose (PPG) that would, in fact, rise steadily with WBIR evolving. Thus, the post prandial insulin (PPI) would also rise steadily until the pancreatic insulin secretory response may possibly start to be impaired at near the end of the IR-III stage. Given that PI concentration usually wanes gradually with the metabolism progressing, the fasting plasma insulin (FPI) would be attenuated significantly from PPI, but both would evolve in similar patterns, as depicted in Fig 2(A).

4.2. Body-Weight Evolution

Insulin plays a pro-anabolic role in the fed state and then an anti-lipolytic role in the fasted state[1, 31]. This concept would be useful to understand how the body weight is affected by the WBIR dependent evolution of PI. The MIR in the IR-I stage would not only elevate the PI (both PPI and FPI) but also effectively redistribute some of the excess PG shunned from the MIR affected muscle tissue to the adipose tissues [32, 33]. The elevated PPI would enhance, in the fed state, adipose fat accumulation by upregulating ADNL as well as entrapping more of the FAs released from TRLs in both the subcutaneous and visceral adipose tissues (pro-anabolic), whereas the elevated FPI would more or less restrict, in the fasted state, adipose lipolysis or fat mobilization (anti-lipolytic). Consequently, body weight would increase very rapidly in the IR-I stage.

In the IR-II stage, development of s-AIR, in addition to the MIR that would now have been matured more, would not only elevate PI further but also effectively redistribute the excess PG – shunned from the subcutaneous adipose tissue as well as the muscle tissue – to the visceral adipose tissue. Consequently, the still AIR-free visceral adipose tissue would build up the fat mass even more rapidly while the AIR affected subcutaneous tissue would start to lose the fat mass by undergoing uninhibited lipolysis, which would lead to nothing but the visceral obesity.

In the IR-III stage, even the visceral adipose tissue would develop AIR and start to undergo uninhibited lipolysis, which inevitably leads to rapid weight loss. In the IR-IV stage, both the subcutaneous and visceral adipose tissue would continue to lose the fat mass until it is to be largely depleted, which would inevitably slow the pace of weight loss significantly. Overall, the body weight would evolve approximately in a kind of an inverted U-shape as depicted in Fig 2(A): it would increase rapidly in the IR-I stage, then saturate slowly in the IR-II stage, then decrease rapidly in the IR-III stage, and then continue to decrease rather slowly in the IR-IV stage [8].

4.3. Obesity Paradox

A noteworthy point in the body weight evolution profile in Fig 2(A) is that the individuals belonging to the IR-I or IR-II stages – likely overweight or obese – would be relatively healthy metabolically simply because at least one or both of the subcutaneous and visceral adipose tissues work properly as a FA reservoir, thereby preventing PG as well as PFA from being elevated too high. By contrast, the individuals belonging to the IR-III or IR-IV stages – likely relatively lean – would be rather unhealthy simply because both the adipose tissues fail to work effectively as a FA reservoir and therefore PG as well as PFA elevates severely. This would explain why some lean individuals have higher mortality than overweight or obese individuals – obesity paradox [34].

In fact, Lee et al. conducted a prospective cohort study, in which all-cause mortality had been traced during a follow up period of 10.5 years, for subgroups of normoglycemia, impaired fasting glucose, newly diagnosed diabetes, and prevalent diabetes, classified at the baseline [35]. And they found that the all-cause mortality varies, regardless of the baseline characteristics, approximately in a U-shape with BMI. More specifically, mortality increased much more steeply with BMI decreasing below the BMI having minimum mortality than it increased with BMI increasing above the BMI having minimum mortality. Conversely, the mortality variation in a U-shape with BMI may support our assertion that the body weight evolves approximately in an inverted U-shape with WBIR evolving.

4.4. Effect of PI on PFA

WBIR dependent, long term variation of PI would also affect directly the evolution of plasma fatty acid (PFA). In principle, PFA concentration would depend on the intensity of adipose lipolysis and delipidation of triglyceride rich lipoproteins (TRLs). In the fed state, the relatively high PPI would inhibit strongly the adipose lipases so that the FA concentration inside the adipocytes drops very low. Consequently, in the fed state, the FAs still remaining in the plasma would diffuse quickly into the peripheral tissues to be either oxidized or esterified into fats, which would lower the postprandial plasma fatty acid (PPFA) significantly. In the fasted state, however, the relatively low FPI would inhibit the adipose lipases not as strongly as in the fed state. Thus, the adipose tissues would undergo lipolysis and release the resultant FAs into the plasma, thereby elevating the fasting plasma fatty acid (FPFA) significantly. This explains why the PPFA is usually lower than the FPFA, as depicted in the Fig 2(B).

4.5. Peculiar Evolution of PFA

An important point here is that the PI is higher in the IR-I stage than in the IS stage, which translates into that the adipose lipases are inhibited more strongly in the IR-I stage than in the IS stage, which in turn translates into that PFA is actually lower in the IR-I stage than in the IS stage, as depicted in Fig 2(B). This also explains why insulin sensitive healthy individuals, including most children, exhibit higher FPA than somewhat insulin-resistant individuals (as in the IR-I or IR-II stage) who are more likely to be overweight or obese [36, 37].

In the IR-II stage, the subcutaneous adipose tissue starts to develop AIR, not only releasing FAs into the plasma by undergoing uninhibited lipolysis but also failing to entrap the FAs released from TRLs. However, the still largely AIR-free visceral adipose tissue would entrap efficiently, especially with the help of significantly elevated PI, most of the FAs shunned or released from the AIR affected subcutaneous adipose tissue. Consequently, PFA elevation in the IR-II stage would be rather modest, as depicted in the Fig 2(B).

In the IR-III stage, however, both the subcutaneous and visceral adipose tissues are affected by AIR, and therefore they not only release FAs into the plasma but also fail to entrap the FAs released from TRLs, thereby elevating the PFA severely. Importantly, the severe elevation of PFA in the IR-III stage will inevitably restrict utilization of PG as the competing energy substrate, which elevates PG significantly as well.

In the IR-IV stage, both the subcutaneous and visceral adipose tissues would no longer be able to support lipolysis as efficiently as in the IR-III stage with the fat mass largely depleted already. Consequently, FPFA in the IR-IV stage would start to saturate and then decline gradually with WBIR evolving, whereas PPFA would elevate steadily as both the adipose tissues are failing ever more to entrap the FAs released from TRLs. This would explain why both the FIRKO and A-ZIP/F-1 mice, lacking adipose tissues working effectively working as the FA reservoir, exhibit PPFA actually higher than FPFA [4, 21].

4.6. Differential Evolution of PPG and FPG

WBIR dependent, long term variation of PI would also affect directly the evolution of PG, but quite differently for the postprandial plasma glucose (PPG) and fasting plasma glucose (FPG). In principle, PG would consist of two distinct components: the exogenous PG attributed to dietary carbohydrate ingested and the endogenous PG attributed to hepatic glucose production (HGP). As long as the pancreatic insulin secretory response is largely intact as in the early stages of WBIR evolution, HGP in the fed state would be suppressed enough by relatively high PPI. This implies that PG in the fed state would consist of mostly exogenous PG, especially in the early stages of WBIR evolution. This in turn implies that PPG would rise steadily with impairment of glucose uptake being enhanced ever more or simply with WBIR evolving, as depicted in Fig 2(B).

The exogenous PG in healthy individuals would be mostly disposed of within the fed state by the tissues still largely IR-free, especially with the help of significantly elevated PPI. This suggests that in the early stage of WBIR evolution FPG would be determined primarily by HGP, which is regulated primarily by FPI – the higher FPI, the more suppressed the HGP, the more lowering FPG. As long as the pancreatic insulin secretory response is largely intact as in the early stages of WBIR evolution, higher PPG would lead to higher PPI, which transitions to higher FPI, which leads to lower FPG.

This line of reasoning would be reduced to: in the case of the early stages of WBIR evolution, FPG would decline with PPG rising, as depicted in Fig 2(B). However, the negative correlation between FPG and PPG would eventually turn positive in the IR-III and IR-IV stage as the severely elevated PFAs restrict PG utilization or HIR makes the liver undergo unsuppressed HGP, thereby elevating severely FPG as well as PPG.

In fact, Hulman et al. traced the PG evolution up to diagnosis of type 2 diabetes in the Whitehall prospective cohort study [38]. We reproduced in Fig 3 the evolution of 2hPG (2 hour plasma glucose) measured by oral glucose tolerance test (OGTT) and FPG for incident diabetics who had been diagnosed of diabetes during the follow up from 1991 to 2013. The 2hPG, which could be considered to approximately represent the PPG, rose steadily with time before diagnosis of diabetes, whereas the FPG initially declined with time and then rose steeply as it becomes closer to

the diagnosis. It is also noteworthy that, far from the diagnosis, the South Asian subgroup with higher FPI than the white subgroup exhibited lower FPG.

An important point here is that the horizontal axis of the time before diagnosis would not necessarily correspond to the WBIR evolution stages introduced in this study, considering that individuals would in general develop diabetes at widely different paces, depending on the concentration of potential IR-inducing agents. A good possibility may be that the farther way from the diagnosis, the more heterogeneous – in terms of WBIR evolution stages – the subjects.

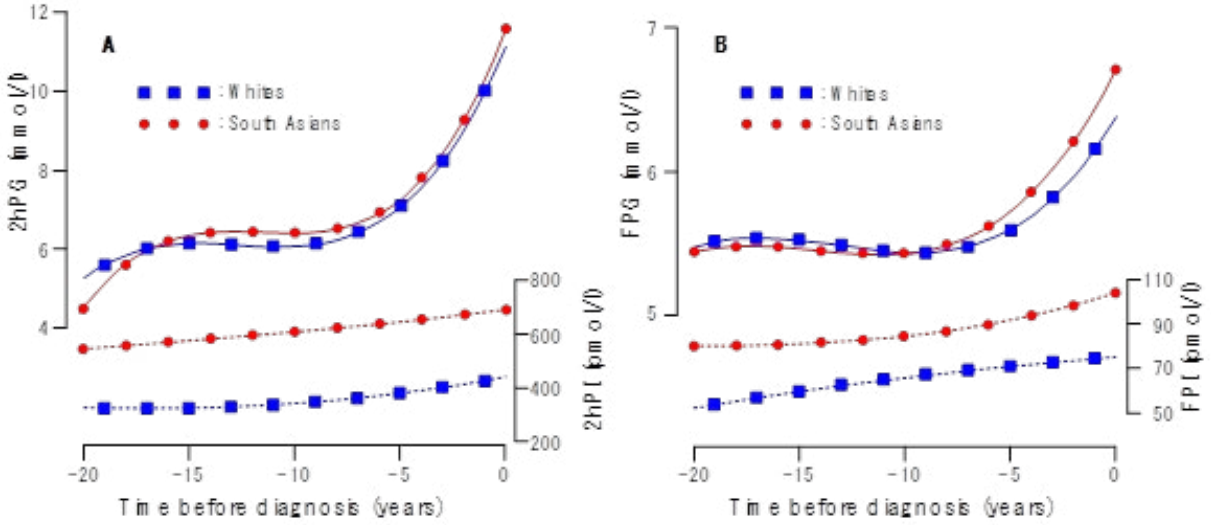

Figure 3: Variation of 2hPG and 2hPI (A), and FPG and FPI (B) before diagnosis of diabetes for the white subgroup and South Asian subgroup

Actually earlier, Tabak et al. had also traced PG evolution with the same Whitehall cohort study [39]. However, they divided the subjects into the subgroup of incident diabetics who had been diagnosed of diabetes during the follow up and the subgroup who had remained nondiabetic, and plotted PG evolution against the time before the end of follow up, rather than the time before the diagnosis. While the FPG in the nondiabetic subgroup remained almost constant throughout the follow up, the FPG in the incident diabetics rose rather slowly in the region far from the end of follow up and then started to rise steeply as it becomes closer to the end of follow up. The positive slope of the FPG with time before the end of the follow up – in contrast to the negative slope with time before diagnosis – may indicate that the subjects were much more heterogeneous (in terms of WBIR evolution stages) in the horizontal axis of the time before the end of follow up than in the horizontal axis of the time before diagnosis.

Meanwhile, Yeni Komshian et al. conducted an insulin suppression test with nondiabetic individuals (possibly belonging to the IR-I and IR-II stages), in which steady state plasma glucose (SSPG) concentration is measured under continuous infusion of insulin and glucose [40]. And they found that FPG was negatively correlated with the SSPG, which may also be considered to represent approximately PPG. This also confirms that the FPG indeed declines with PPG in those who are more likely in the early stages of WBIR evolution. Based on these reasonings, it may be said quite safely that the FPG tends to remain relatively low until very late in the course of diabetes development [41]. An important point here is that diagnosis of diabetes based on FPG would be more likely to give false sense of security when, in fact, WBIR has already advanced significantly. In other words, the practice of diagnosing diabetes based on FPG may possibly tend to prevent early diagnosis.

The most important point regarding the evolution of FPFA and FPG depicted in Fig 2(B) may be that both the FPFA and FPG (the primary and secondary fasting energy substrate, respectively) are actually lower in the weight gaining IR-I and IR-II stages than in the IS stage. The lack of the fasting energy substrates, FPFA and FPG, in the plasma would be more likely to enhance the hunger felt in the fasted state likely leading to overeating – as well as more likely to let individuals avoid intense physical activity. The likelihood of overeating and physical inactivity would easily lead to the positive energy balance that is essential for weight gaining [42].

4.7. Validation of four-stage WBIR Evolution

The four stage metabolic evolution from rapid weight gain to visceral obesity, then to rapid weight loss, and then to full-blown diabetes appears to comply rather well with the natural development history of diabetes [9]. This may conversely validate the four-stage WBIR evolution model. In reality, the validity of the four-stage WBIR evolution model would rest primarily on the validity of the postulation that tissue specific IRs develop in the order of MIR, s-AIR, v-AIR, and HIR. A simple way to check its validity may be to assume a different order of development and then to compare the predicted metabolic outcomes with the more familiar observations. For instance, if AIR develop first – as is the case with the FIRKO mice – WBIR evolution would start with rapid weight loss, rather than rapid weight gain. And if HIR develop first – as is the case with the LIRKO mice – severe fasting hyperglycemia would be observed from the early stages of WBIR evolution. And if v-AIR precede s-AIR, visceral obesity would never be observed. And if all the MIR, s-AIR, v-AIR, and HIR develop simultaneously, both PG and PFA rise steadily with WBIR evolving, whereas body weight would decrease

steadily. A noteworthy point is that, in type 1 diabetics with no or little insulin secretion, insulin action would be missing in the whole body simultaneously, which would make the metabolic disruptions due to MIR, s-AIR, v-AIR, and HIR occur almost simultaneously. This may explain why untreated type 1 diabetics become emaciated quickly, possibly without showing any sign of visceral obesity.

4.8. Surrogate Measures for WBIR Evolution

If the four-stage WBIR evolution model were indeed valid, there would exist some surrogate measures that represent approximately the degree of WBIR evolution fairly well. A good candidate would be the PPG that rises steadily with WBIR evolving [40, 41, 43, 44]. On the other hand, the FPG would be an utterly poor surrogate measure simply because it declines with WBIR in the early stages of evolution. Neither the PPI nor FPI would be a good surrogate measure – they tend to saturate or decline in the later stages of WBIR evolution . The FPFA would not be a good surrogate measure, either – it dips low in the IR-I and IR-II stages and starts to saturate or decline with the adipose fat mass largely depleted. The fasting plasma triglyceride (FPTG) would not be a good surrogate measure, either – it saturates in the IR-IV stage. Body weight or BMI would be an utterly poor surrogate measure – it evolves approximately in an inverted U-shape with WBIR evolution.

Probably, the best surrogate measure may be the HbA1c, which is known to reflect the time averaged PG in the preceding 10-12 weeks and thus is considered to take into account the effect of both the fasting glycemia and postprandial glycemia. In general, however, HbA1c correlates better with PPG than FPG [44].

5. Debunking of the Lipid-Induced Insulin Resistance (LIIR)

Even though the four stage WBIR evolution model appears to be largely validated, it does not tell anything about IR-inducing agents or mechanisms. A widespread belief is that IR is induced by lipids. A core argument of the so called lipid-induced insulin resistance (LIIR) is that obesity or the adipose fat mass induces IR either directly or indirectly by contributing excess FAs to the plasma so that the elevated PFAs somehow interfere the insulin action in cells or tissues. It is noted, in reality, that the elevation of PFA itself has an effect of effectively elevating PG – Randle cycle or glucose-FA cycle which apparently lends support to LIIR [22,23,45].

5.1. PFA Elevation, more likely an Effect of AIR

In fact, Karpe et al. extensively reviewed literatures only to find that the correlation between the body weight and PFA is not very straightforward [45]. For instance, some obese or overweight individuals exhibit PFA actually lower than the average, whereas lean individuals exhibit a wide range of PFA (from below to well above the average). This is, in fact, largely in accordance with the heuristically drawn PFA evolution depicted in Fig 2(B). Thus, the belief that obesity first elevates PFA and then induces IR can hardly be supported.

On the other hand, if elevation of PFA indeed has a property to induce IR, insulin-sensitive individuals (as in the insulin sensitive (IS) stage) who exhibit relatively high PFA and are more likely to be lean would develop IR more readily than already insulin-resistant individuals (as in the IR-I or IR-II stage) who exhibit relatively low PFA and are more likely to be overweight or obese. Certainly, this argument would be utterly absurd.

A serious problem with LIIR is that it does not tell which tissue-specific IR is to be induced by obesity or lipids. From the perspective of WBIR evolution, however, MIR in the IR-I stage contributes to weight gaining or obesity – not the other way around – by not only elevating PI but also effectively redistributing some of the excess PG shunned from the MIR affected muscle tissue to adipose tissues. On the other hand, the AIR, for instance, in the IR-III stage leads to rapid weight loss by letting adipose tissues undergo uninhibited lipolysis and simultaneously elevating PFA severely as well. That MIR contributes to weigh gaining whereas AIR leads to rapid weight loss can hardly be explained by LIIR.

5.2. Ectopic Fat, More Likely an Effect of AIR, too

Another branch of LIIR is the notion that ectopic fats induce IR. For instance, many researchers believe that HIR is attributable to the ectopic fats deposited in the liver [46, 47]. However, fundamentals of physiology tell that ectopic liver fat appears to be more likely an effect of AIR in particular. In more detail, AIR elevates severely PFA by making the adipose tissues not only undergo uninhibited lipolysis but also unable to entrap the FAs released from TRLs. The severely elevated PFAs – shunned by the AIR-affected adipose tissues – would easily diffuse into peripheral tissues, notably the liver and muscles. Then, a fraction of them would subsequently be esterified into ectopic fat [20]. A supporting evidence is that the FIRKO and A-ZIP/F-1 mice – both lacking the adipose tissue working properly as a FA reservoir and therefore exhibiting almost the same phenotype – exhibit a significant amount of ectopic liver fats [4, 21].

Ectopic liver fats may also result from enhancement of hepatic de novo lipogenesis (HDNL) [47]. It is noted, however, that enhanced HDNL itself may also be attributable to AIR. In more detail, AIR elevates not only PFA but also PG, thereby significantly enhancing hepatic glucose uptake and subsequently HDNL – only if the hepatic insulin signaling is still largely intact or the liver is not yet affected by HIR. This implies that enhancement of HDNL is, in a sense, an indication that liver is still responding properly to insulin or largely free from HIR. The enhancement of HDNL would inevitably lead to enhancement of VLDL generation and secretion to the plasma. However, the severely elevated PFAs due to AIR would hamper VLDL delipidation which would in turn hamper VLDL secretion to the plasma, which would certainly contribute to ectopic liver fat deposition [16].

Based on this reasoning, increased ectopic liver fat deposition, due to either enhancement of HDNL or increased hepatic influx of FAs, would seem to have more to do with AIR, rather than HIR. A noteworthy point is that a hallmark of HIR is, in reality, the unsuppressed HGP or fasting hyperglycemia, rather than ectopic liver fat deposition.

5.3. Ectopic Fat Deposition Contributing to PFA Homeostasis

A serious problem with the notion that ectopic fats induce IR

is that even healthy individuals, who are more likely to be free from IR in general, also accumulate a considerable amount of intramyocellular lipid (IMCL) ectopic muscle fat – especially when they fast, engage in prolonged exercise, or rely on low carbohydrate diet (LCD) [48-51]. Fasting would lower the FPI significantly, which would in turn enhance adipose lipolysis significantly thereby significantly elevating PFA and increasing FA flux into muscle tissues, which would in turn inevitably increase IMCL deposition significantly. Prolonged exercise would also enhance adipose lipolysis significantly, possibly with the help of elevated epinephrine, thereby elevating PFA significantly and subsequently increasing IMCL deposition significantly. LCD would minimize the postprandial insulin secretion and thus lower FPI significantly, which would in turn enhance adipose lipolysis significantly, thereby elevating PFA significantly and subsequently increasing IMCL deposition significantly.

The finding that even healthy individuals accumulate a considerable amount of ectopic fats may suggest that ectopic fat deposition is, in reality, a body's homeostatic response to prevent PFA from elevating too high. In order to achieve PFA homeostasis more efficiently, the ectopic fats deposited usually in the fasted state should be oxidized as early as possible in the ensuing fed state, which would inevitably tend to delay glucose oxidation and thereby apparently elevate PG significantly especially in the postprandial period. Kanamori et al. conducted an interesting experiment, in which healthy subjects were fed on high carbohydrate diet (HCD) on day 1 (D1) and D2, and switched to low carbohydrate diet (LCD) on D3, and switched back to the same HCD on D4 [52]. Interestingly, however, PPG was elevated much higher on D4 than on D2, even though the subjects ingested the same HCD on those two days.

Proponents of LIIR may argue that the apparent impairment of glucose tolerance (or elevation of PPG) on D4 serves as evidence that the elevated PFA or increased ectopic fat deposition on D3 (due to LCD) induces IR. However, given that IR develops usually over a long span of time, the apparent impairment of glucose tolerance after ingesting LCD for only a day can hardly be attributable to IR development. If IR were induced simply by a change of diet for only a day, it could be reversed easily by correcting diet for only a few days. Similarly, the apparent impairment of glucose tolerance after exercise or fasting can hardly be attributable to IR development, considering especially that fasting had once been prescribed as an important option for treating diabetes and exercise is still widely practiced for managing diabetes [53].

6. Proposing of the Glycation-Induced Insulin Resistance (GIIR)

Now that LIIR is largely refuted – especially in the perspective of the four-stage WBIR evolution model – it would be essential to find an appropriate IR-inducing model or mechanism that is compatible to the WBIR evolution. A prominent aspect of WBIR evolution is that PPG is elevated ever faster with WBIR evolving. A speculation is that hyperglycemia may have an inherent property to induce or worsen IR. For instance, even type 1 diabetics, who have little or no insulin secretion and therefore are inevitably exposed to severe hyperglycemia, also develop severe IR [54, 55]. The A-ZIP/F-1 mice, lacking adipose tissues working as a FA reservoir and therefore inevitably exposed to severe elevation of PG as well as PFA, eventually develop diabetes, but surgical implantation of wild type adipose tissue in the transgenic mice not only normalizes PG but also reverses the diabetes [56]. Moreover, most diabetes management or treatment plans, including exercise and administration of anti-diabetic medications (ADMs), make a point of lowering PG.

A reaction activated especially in hyperglycemic physiological condition is glycation or non enzymatic glycosylation, in which glucose and its glycolytic derivatives, such as glyoxal and methylglyoxal, react non enzymatically with proteins and form covalently bonded adducts [57, 58]. If hyperglycemia were sustained long enough, the glycation adducts would rearrange themselves into nonreversible advanced glycation end products (AGEs).

6.1. Protein Glycation Deforming Polypeptide Chain

An important aspect of the glycation reaction is that glycation adducts are formed preferentially on the positively charged (of either polarized or ionic) constituents of proteins, such as N-terminus amino group and residues of lysine, arginine, and cysteine. No less importantly, glycation adducts formed on the positively charged constituents appear to effectively neutralize the positive charges [59]. In this case, the attractive forces between the neutralized (originally positively charged) residues and the nearby negatively charged residues would disappear, which would inevitably unfold locally the polypeptide chain. Importantly, the proteins with both the charge distribution and conformation disrupted significantly can hardly function properly.

Another important aspect of the protein glycation is that cellular proteins in general are glycated more readily than extracellular proteins in the plasma or the interstitial fluid [60]. Plasma membrane proteins on the surface of the cells in tissues, certainly a category of cellular proteins, may particularly be susceptible to glycation, simply because they would be exposed not only to glucose in the interstitial fluid but also to the very potent glycating agents, such as glyoxal and methylglyoxal that may be produced as glycolytic byproducts inside the cells [61].

6.2. Glycation-Induced Insulin Resistance (GIIR)

An example of the plasma membrane proteins is the insulin receptor that mediates insulin action in the cell. If the insulin receptor protein is glycated enough so that its charge distribution and conformation are not compatible to those of insulin, insulin can hardly bind properly to glycated insulin receptors and thus fail to initiate insulin signaling. The failure of insulin to initiate insulin signaling, as observed in the mice with insulin receptors knocked out, as a result of glycation of the insulin receptor or other proteins directly involved in downstream insulin signaling would give rise to nothing but the glycation-induced insulin resistance (GIIR) [2-4]. Actually, the authors had proposed this IR induction mechanism elsewhere [62].

An important point is that glycation reaction is a process that proceeds rather slowly over a relatively long span of time, ex-

actly like WBIR evolution, whereas the glucose-FA cycle proceeds rather quickly [48]. Thus, the possibility for the glycation reaction to be involved in IR development or WBIR evolution is much higher than that for the glucose-FA cycle to be involved. Another revealing observation is that metformin – probably the most widely prescribed oral hypoglycemic agent (OHA) – is known to have an effect of inhibiting glycation process [63-65]. Conversely, this may support that glycation reaction is involved in IR development or WBIR evolution.

6.3. Hyperglycemia and GIIR in a Vicious Circle

GIIR would enhance hyperglycemia further by impairing glucose uptake, which would in turn enhance GIIR further, establishing a positive feedback loop in which hyperglycemia and GIIR reinforce each other in a vicious circle. This means PG is elevated ever faster with the vicious circle going. Meanwhile, the four stage WBIR evolution model also predicts that PG or time averaged PG rises ever faster with WBIR evolving. This parallel may indicate that GIIR is the very IR-inducing mechanism behind the WBIR evolution. An important point regarding the vicious circle may be that hyperglycemia is the cause as well as an effect of GIIR. In contrast, GIIR is only an effect of hyperglycemia. This suggests that hyperglycemia is the very fundamental force driving the WBIR evolution or vicious circle. The four stage WBIR evolution driven by hyperglycemia could be described as below.

6.4. Sequential Progression of Tissue-Specific GIIR

Hyperglycemia, the fundamental driving force for WBIR evolution, can easily be achieved, at least in the postprandial period, even in the insulin-sensitive (IS) stage by increasing postprandial glycemic load or increasing carbohydrate intake. With postprandial hyperglycemia achieved regularly for a period long enough, for instance, by relying on high carbohydrate diet (HCD), GIIR would start to develop first preferentially in the muscle tissue with a relatively low cell turnover, in which average cells would have been exposed longer to hyperglycemia.

With the muscle tissue gradually developing IR (more specifically MIR), the IS stage would gradually transition to IR-I stage. Meanwhile, MIR in the IR-I stage would impair the muscle glucose uptake and therefore enhance postprandial hyperglycemia further, thereby accelerating WBIR evolution further. The hyperglycemia enhanced by MIR would eventually make even the subcutaneous adipose tissue with a even higher cell turnover start to develop gradually GIIR (more specifically s-AIR).

With s AIR developing gradually, the IR-I stage would gradually transition to the IR-II stage, in which MIR and s-AIR would enhance hyperglycemia further, thereby accelerating WBIR evolution further. Consequently, even the visceral adipose tissue with a higher cell turnover would start to develop gradually GIIR (more specifically v-AIR).

With v-AIR developing gradually, the IR-II stage would gradually transition to the IR-III stage, in which severe elevation of PFA would enhance hyperglycemia even more severely by restricting PG utilization. Consequently, even the liver with a very high cell turnover would start to develop gradually GIIR (more specifically HIR). With HIR developing gradually, the IR-III stage would gradually transition to IR-IV stage, in which HIR would make the liver undergo unsuppressed HGP, thereby enhancing hyperglycemia even more and accelerating WBIR evolution further.

6.5. Glycation Free Adducts and Glycation Adduct Residues

An indisputable evidence for glycation reaction being active in hyperglycemia would be a disproportionately high plasma level of glycation free adducts – glycated amino acids or short peptides circulating freely in the plasma – observed in diabetics [66, 67]. Glycation free adducts that are broken off the glycated proteins undergoing proteolysis may first enter the interstitial fluid that bathes the cells in tissues and then eventually be collected in the blood plasma.

On the other hand, the glycation adduct residues that are still covalently bonded to the amino acid residues constituting the still functioning proteins in tissues would not be detected easily. Nevertheless, the glycation adduct residues would be extremely harmful or toxic simply because they could disable the host proteins in cells or tissues. By contrast, we speculate against the common belief, glycation free adducts may be considered only risk markers, rather than risk factors, not only because they would no longer affect the functioning of the cells or tissues but also because they would be mostly excreted in urine [66, 67].

6.6. Glycation Reaction Possibly Involved in Metabolic Syndrome

MIR, s-AIR, v-AIR, and HIR may be considered to be associated with each other, simply because they are all induced by glycation of the proteins involved in insulin action in the muscle tissue, subcutaneous adipose tissue, visceral adipose tissue, and liver, respectively. It is noted, however, that even though MIR, s-AIR, v-AIR, and HIR are associated with each other, they would not necessarily develop simultaneously.

If the proteins involved in insulin action in the muscle tissue, adipose tissue, and liver were glycated severely enough in hyperglycemia as to give rise to impairment of insulin action in the respective tissues or organs, some of the proteins involved in insulin generation or secretion in the pancreas could also be glycated severely enough as to give rise to impairment of insulin generation or secretion. A revealing observation is that chronic hyperglycemia is known to trigger loss of pancreatic beta cell differentiation, consequently impairing insulin generation or secretion [68]. This may explain why impairment of pancreatic insulin secretory response is also associated with IR in general or hyperglycemia.

Similarly, under sustained hyperglycemia, some critical proteins in still other tissues or organs, such as cardio/cerebral endothelia, nephrons, neurons, and retina can also be glycated severely so that they are deteriorated enough functionally or structurally as to make them exhibit particular symptoms associated with cardio/cerebral vasculopathy, nephropathy, neuropathy, and retinopathy, respectively. This may explain why a cluster of disorders or diseases that are often collectively referred to as the

metabolic syndrome such as obesity, diabetes, cardio/cerebral vasculopathy, nephropathy, neuropathy, and retinopathy appear to be associated with each other and then with hyperglycemia [69].

6.7. Glycation Reaction and HbA1c

Perhaps one of the best-known examples of glycated proteins may be the glycated version of hemoglobin, often referred to as HbA1c, which is formed inside the red blood cells during the life span of three to four months [70]. As well known, the level of HbA1c represents the time averaged PG concentration in the preceding 10-12 weeks. Certainly, glycation reaction is behind the formation of glycated hemoglobin HbA1c, as it is insisted (in this study) to be behind the WBIR evolution. It would then hardly be incidental that the HbA1c level is one of the best surrogate measures of WBIR or diabetes evolution.

6.8. GIIR in Type 1 Diabetes

Lastly, the concept of GIIR can also be applied to type 1 diabetes in which insulin secretory response is largely missing. In the case of untreated type 1 diabetics, metabolic disruptions due to MIR, s-AIR, v-AIR, and HIR would occur simultaneously – no insulin action in the whole body, exactly as in the IR-IV stage – thereby elevating PG severely and enhancing GIIR severely. This explains why delay of insulin injection therapy in type 1 diabetes would rapidly aggravate the disease, only to increase the dose of insulin required [54, 55].

7. Conclusion and Discussion

We have proposed four-stage WBIR or diabetes evolution model, based on the fundamentals of physiology as well as careful evaluation of relevant literatures. The four-stage metabolic evolution from rapid weight gain to visceral obesity, then to rapid weight loss, and then to full-blown diabetes complies well with the natural development history of diabetes, and resolves many controversies regarding obesity or diabetes, including visceral obesity, obesity paradox, and dawn phenomenon that have long remained metabolic puzzles. In addition, the model refutes the LIIR but supports, instead, the GIIR proposed in this study.

The single most important conclusion in this study is that hyperglycemia is the main driving force or primary risk factor for WBIR evolution. Hyperglycemia and GIIR reinforce each other in a vicious circle, thereby driving WBIR to evolve ever more rapidly. A speculation is that the glycation reaction activated in hyperglycemia may act as the common thread connecting a cluster of diseases or disorders that are collectively referred to as the metabolic syndrome, such as obesity, diabetes, cardio/cerebral vasculopathy, nephropathy, neuropathy, and retinopathy. Glycation reaction enhanced ever more with WBIR evolving would deform ever more critical proteins in various organs or tissues, thereby letting ever more symptoms or disorders associated with hyperglycemia or diabetes be manifested with WBIR evolving.

If WBIR were driven by hyperglycemia, the most obvious approach to delay or reverse WBIR evolution would be to alleviate hyperglycemia, which is, in fact, the primary goal of diabetes management or treatment. Obviously, the most fundamental way to alleviate hyperglycemia is to reduce postprandial glycemic load by curtailing carbohydrate intake. One of the most significant findings in this study is that weight gaining or obesity has a beneficial effect of alleviating hyperglycemia, the main driving force for WBIR evolution – even the visceral obesity is known to have protective effect [71]. Enhancement of ADNL associated with weight gaining, as observed in the IR-I stage, would certainly alleviate hyperglycemia simply because it is one of the most important glucose disposal pathways activated in the hyperglycemia. On the other hand, weight loss associated with AIR, as observed in the IR-III or IR-IV stage, would have an effect of aggravating hyperglycemia – AIR inhibits the glucose disposal pathway, ADNL – and thus hardly be beneficial for health.

Weight gaining or obesity that has an effect of alleviating hyperglycemia and thus delaying WBIR evolution can hardly be considered a risk factor per se. However, it would still hardly be beneficial overall for health. This suggests strongly that behind the weight gaining or obesity lies an independent risk factor, which is none other than the hyperglycemia. This in turn suggests that weight loss can be achieved healthily by alleviating hyperglycemia.

For instance, the rapid weight gaining in the IR-I stage can be reversed by alleviating postprandial hyperglycemia or by reducing postprandial glycemic load. The alleviation of postprandial hyperglycemia would decrease postprandial insulin secretion, which subsequently alleviates hyperinsulinemia. The alleviation of hyperinsulinemia coupled with the alleviation of postprandial hyperglycemia would restrict significantly ADNL in the fed state but enhance more or less adipose lipolysis in the fasted state, thereby likely leading to weight loss. Moreover, enhancement of adipose lipolysis and HGP due to alleviation of hyperinsulinemia would respectively lead to significant elevation of FPFA and FPG, the fasting energy substrates. The relative abundance of the fasting energy substrate in the plasma would be more likely to relax the hunger felt in the fasted state, thereby leading to overeating – as well as let individuals accommodate intense physical activity relatively easily. The likelihood of moderate eating and intense physical activity would lead to negative energy balance essential for weight loss [42, 72].

Alleviation of postprandial hyperglycemia in the IR-I stage for long enough to reduce the body weight to the level expected in the IS stage may also reverse WBIR from the IR-I stage to the IS stage. This would be in line with the previous argument that sustaining postprandial hyperglycemia for long enough in the IS stage, for instance, by relying on high carbohydrate diet (HCD) would not only promote WBIR to the IR-I stage but also increase the body weight to the level expected in the IR-I stage. An important point here is that the weight loss achieved by alleviating hyperglycemia would be of a healthy kind since it would help to secure more of the storage capacity of the FA reservoir of adipose tissues. By contrast, the weight loss associated with AIR, as observed in the IR-III or IR-IV stage, is of a very unhealthy kind since it would shrink further the storage capacity of the FA reservoir as well as effectively enhance hyperglycemia further.

If weight loss can be either achieved healthily by alleviating hyperglycemia or incurred very unhealthily by being afflicted by AIR, body weight or body mass index (BMI) would hardly be a good surrogate measure of healthiness in general. This in turn suggests that it would not be a good idea to plot health related variables against BMI put in the horizontal axis, as observed so often in literatures. For instance, when we plot mortality against BMI put in the horizontal axis, the graph would in general have approximately a U-shape or J-shape, which confirms nothing but the obesity paradox [35, 73-76].

Notwithstanding the obesity paradox so commonly observed, however, many researchers may still firmly believe that weight gaining or obesity per se is an absolute risk factor. This ill founded belief could easily let some researches be biased in interpreting their experimental results. For instance, the researchers, probably from the same institute, had made conflicting assessments of the AIR model of FIRKO mice in the studies reported in 2002, 2003, and 2016. In more detail, the 2002 study insisted that FIRKO mice were protected against obesity and obesity related glucose intolerance and the 2003 study insisted that the mice could extend longevity [77, 78]. On the other hand, the 2016 study found that the FIRCO mice quickly develop diabetes as well as nonalcoholic fatty liver disease (NFLD) [5]. According to our understanding, however, the AIR in the FIRKO mice is a very lethal disorder that elevates PG severely and therefore drives WBIR to evolve very rapidly. This tells clearly that the assessment in the 2016 study is much closer to the truth than those in the 2002 and 2003 studies.

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