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# Randle Cycle as Applied to Diabetes Mellitus Type 2 'Spruce the Basement before Dusting the Super-structure'

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***Author's contribution***

*The sole author designed, analyzed and interpreted and prepared the manuscript.*

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## ABSTRACT

Randle cycle (1963) is about substrate competition between products of glycolysis and β–oxidation to capture the citric acid cycle for further oxidation. Acetyl –CoA, the end product of both the energy metabolisms, when accumulates in mitochondrial matrix beyond the oxidative capacity of the citric acid cycle, far reaching consequences take place than simple substrate competition, inhibition of pyruvate dehydrogenase (PDH), inhibition of glycolysis and preferential passage of β-oxidation products through citric acid cycle, as conceived by Randle. It is shown that citric acid cycle is equally shut off for both products of energy metabolism initially. Hence, the question of substrate competition between them does not arise. How the preferential passage of β-oxidation products occur is explained by a different mechanism than what Randle put forward. The final common pathway to either of β-oxidation or lipogenesis is- acetyl CoA carboxylase (ACC)-melanoyl- CoA-CPT 1. The final result depends on whether ACC is stimulated or inhibited inhibition results in β-oxidation and stimulation results in lipogenesis. Randle contention is not true because, simultaneously, AMPK is also inhibited which inhibits in turn the β -oxidation The proposed hypothesis suggests that low substrate for ACC i.e. Plasma acetyl- CoA, which is carboxylated to

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melanoyl- CoA is responsible for switch of energy metabolism to β-oxidation independent of AMPK. To corroborate the proposed mechanism, a low pyruvate level, an additional block in the glycolytic pathway at the level of Pyruvate kinase (PK) and involvement of hexose monophosphate shunt (HMP shunt) are proposed with objective evidence, supporting the same.

*Keywords: Randle cycle; PDK-Pyruvate dehydrogenase kinase; PK- Pyruvate kinase; PC – Pyruvate carboxylase; CPT- Carnitine palmitoyltransferase; ACC- Acetyl–CoA carboxylase.*

## 1. INTRODUCTION

Randle cycle is about the substrate competition between end products of β -oxidation of the fatty acids and glycolysis in the mitochondrial matrix to gain entry into the citric acid cycle and consequent inhibition of the later by the former [1]. It is a biochemical mechanism that controls fuel selection and adaptation of the substrate supply and demand in normal tissues, coordinating with hormonal control of substrate concentration. There is dynamic adaptation between the tissues that supply the substrate (ex FA by adipose tissue), tissues that utilize the substrate as fuel (muscle) and hormone that control both (glucagon/epinephrine) during exercise [2]. It introduced a new dimension of control of the energy metabolism by adding a nutritionally mediated fine tuning on the top of the more course coarse hormonal control. Inhibition of one nutrient over the other, independent of hormonal mediation was also demonstrated. It was further shown by Randle et al, that chronic exposure to FAs causes insulin insensitivity, promoting β –oxidation.

The substrate competition referred to above is due to acetyl-CoA being the final product of both the metabolism competing for oxaloacetate (OA), the common substrate in the first step of the citric acid cycle, the availability as such of OA being limited. As a result it is conceived by Randle, that the glycolytic pathway is suppressed at the level of conversion of pyruvate into acetyl- CoA by the enzyme PDH, by increase in ratios of acetyl-CoA/ CoA and NADH/NAD .The Increase in these ratios is not only the result of glycolysis but β -oxidation also. Randle proposed varying levels of inhibition in glycolytic pathway, being maximal at the level of Pyruvate dehydrogenase (PDH) and in decreasing levels at phosphofructokinase (PFK), both of which are accepted. His further contentions that because of block at PFK, the levels of G-6P increased resulting in inhibition of hexokinase and consequent decrease in cellular uptake of glucose have been disproved. The first challenge to reduced glucose uptake by the cell due to inhibition of hexokinase came from the experimental conclusions of Roden et al. [3]. It is now established that the reduced uptake of glucose is because of failure of translocation of GLUT 4 to the cell membrane [4]. Even the varying blocks suggested by Randle, were quantified as being about 15 to 25% at the glucose uptake level, 40 to 60% at PFK level and complete inhibition at PDH level [5]. It was established experimentally that the Randle cycle worked in whole animals as well as in human beings [6].

The proposed hypothesis: -

The various events are depicted under Mitochondrial and cytoplasmic events.

The mitochondrial events:-

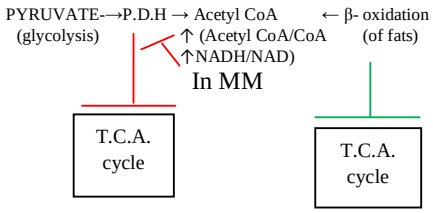
**Step 1:**

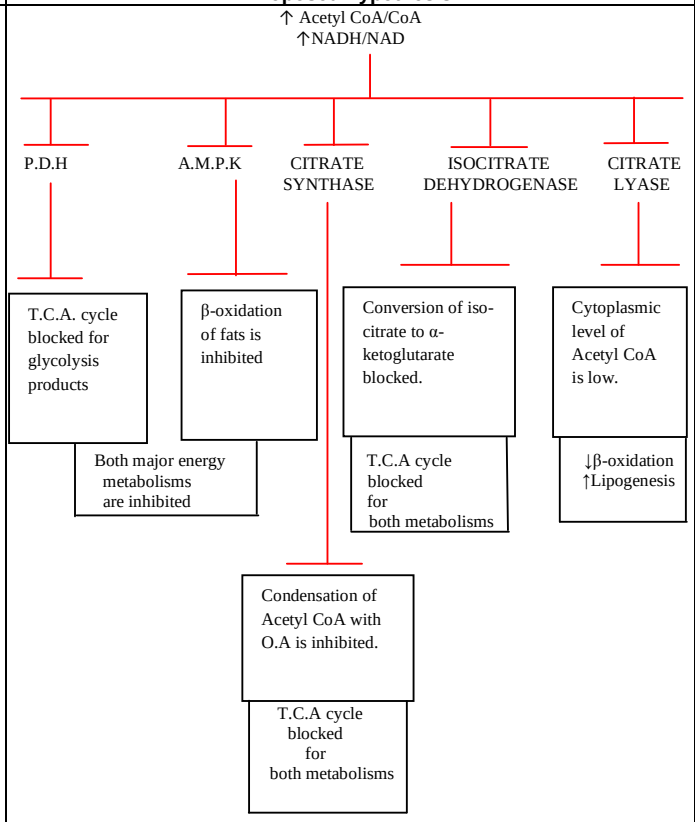
Accumulation of acetyl –CoA in mitochondria: - Tables 1 and 2.

Acetyl CoA, the end product of both glycolytic pathway and beta oxidation accumulates in the mitochondrial matrix. When the accumulated acetyl -CoA in the mitochondria exceeds the oxidative capacity of citric acid cycle, feedback inhibition of PDH, through increased ratios of acetyl -CoA/CoA and NADH NAD occurs as contended by Randle.

But the same increase in these ratios also cause inhibition of AMPK, Citrate synthase, Isocitrate dehydrogenase and citrate lyase and stimulates GN, some of the facts ignored by Randle .The AMPK which is in stimulated in the presence of glucagon excess inactivates ACC by phosphorylation. With inhibition of AMPK now, ACC is dephosphorylated and ACC is active. This increases malonyl -CoA level stimulating lipogenesis, by inhibiting β -oxidation. This is exactly opposite of what Randle proposed. The combined effect of inhibition PDH and AMPK is inhibition of glycolysis and β - oxidation, the two major catabolic energy pathways, GN and lipogenesis and the two anabolic path ways are stimulated by AMPK inhibition.

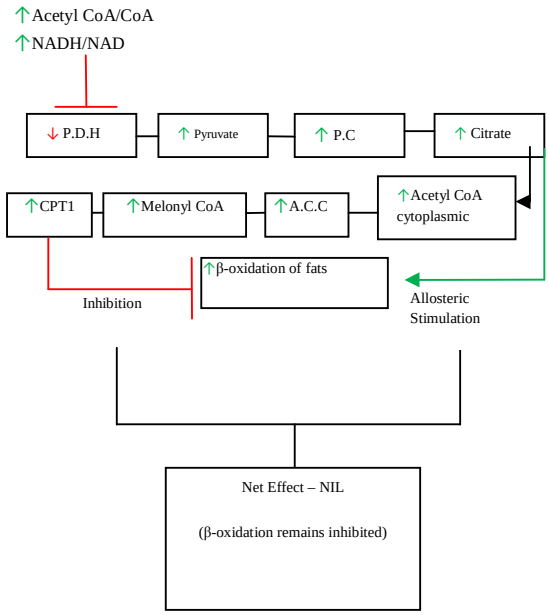
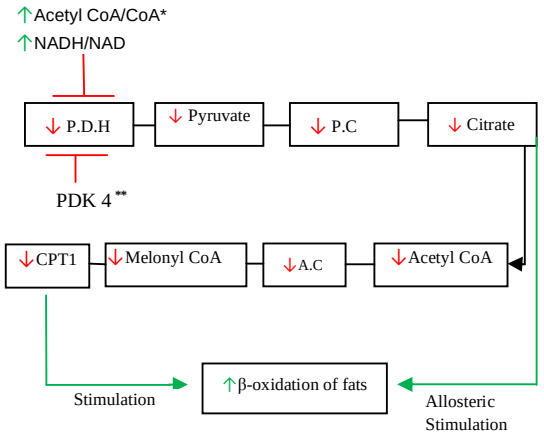
**Table 1. Affect of increased ratios of Acetyl CoA/CoA and NADH/NAD**

<table>
<tr><th>Randle cycle</th><th>Proposed hypothesis</th></tr>
<tr><td>


<br><br>NB: - When Acetyl-CoA, the end products of both glycolysis and B-Oxidation, there is competition for the substrate, Oxalo- acetate.<br><br>According to Randle only PDH is inhibited by the increased ratios of Acetyl-CoA/CoA& NADH/NAD, blocking the entry of glycolytic products in to Kerb's cycle.
</td><td>


<br><br>NB :-<br>The same increased ratios in fact inhibit multiple enzymes whose consequences are dip [cted above].<br><br>
Fate of Acetyl CoA already Accumulated in mitochondrial matrix.
<table>
<tr><th>From glycolysis</th><th>From β-oxidation</th></tr>
<tr><td>↓P.D.H ↑P.C<br><br>G.N<br><br>Started</td><td>↓A.M.P.K<br><br>• G.N<br>• Lipogenesis and<br>• Ketogenesis<br>Are started</td></tr>
</table>
</td></tr>
<tr><td colspan="2">NB: Red line/arrow- indicates inhibition/decreased concentration<br>Green line/arrow- indicates stimulation/increased concentration</td></tr>
</table>

**Table 2. Post PDH inhibition events- Preferential initiation, perpetuation and access to T.C.A cycle of β-oxidation products over glycolytic products**

| Case 1:- ↑Pyruvate ↑Citrate (current view) | Case 2:- ↓Pyruvate ↓Citrate (proposed hypothesis) |
|---|---|
|  |  |
| **If pyruvate is increased consequent to PDH inhibition, the end result should have been stimulated B-Oxidation as contended by Randle, but actually the B-Oxidation is inhibited. Contention of Randle cyclethus not fulfilled, if pyruvate is actually increased initially.** | **Contention of Randle cycle fulfilled If initial pyruvate level is low.**<br>*** The inhibitory effect lasts only until the ratios are reversed.**<br>****The inhibitory effect is constant and continues in starvation/DM2.** |

Increase acetyl CoA / CoA and NADH/NAD ratios also inhibit the Isocitrate dehydrogenase, the enzyme catalyzing the irreversible step of converting isocitrate to alfa keto glutarate. Inhibition of citrate synthase inhibits the synthesis of citric acid. This together with inhibited citrate synthase by the same increased ratios ensures that the citric acid cycle is blocked for entry of either of the products under consideration. Inhibition of citrate lyase decreases cytoplasmic acetyl- CoA. which is the starting point of glucogenic fatty acid synthesis.

**Step 2:**

Initiation of GN, lipogenesis and ketogenesis: -

The GN and ketogenesis sustain the energy supply to vital organs like brain when both the major energy producing pathways are inhibited temporarily.

A) The GN: - The AMPK inhibition by the increased acetyl CoA/ CoA and NADH / NAD (which stimulates anabolic metabolism) and inhibition of PDH (which activates PC) signals the start of GN. Glucagon, by lowering of the level of FBP blocks glycolysis. The acetyl Co -A produced already from the PDH reaction cannot be converted back to pyruvate, as PDH reaction is irreversible. It can not be processed through the citric acid cycle as the same is shut off. Hence the glycolytic flux is re- routed through GN pathway by PC. Further, glucagon acting through c AMP cascade causes higher level of phosphorylase activity and a lower level of

glycogen synthase activity resulting in the production of high glucose levels by the liver.

B) Ketogenesis:- Since the accumulated acetyl -CoA cannot enter the citric acid cycle, the flux of β –oxidation which is already in mitochondrial matrix, is re -routed through ketogenic pathway. This produces acetone (and other ketone bodies) ultimately, capable of crossing blood brain barrier to reach the brain, to sustain its activity. They also serve as metabolic fuel for other tissues which can utilize them as source of energy. This explains the facts that ketogenesis accompanies sometimes GN. They are also responsible for glucose sparing effect when glucose is in short supply.

C) Lipogenesis: - Is initiated by AMPK, PKA (protein kinase A and PPAR Gama. It is a known fact that the glucogenic, de novo synthesis of FA is deranged in starvation.

a) The three NADPH producing enzymes I.e. glucose 6 phosphate dehydrogenase (G-6PDH), 6- phospho gluconic acid dehydrogenase, and isocitrate dehydrogenase are shown to have reduced activity within 24 hours of starting starvation [7]. After a week's fasting t glyceride synthesis was decrease by 70% in adipose. This decrease was evident even from 5th day of the fasting [8].

b) Acetate appears to be the substrate of choice in starvation for synthesis of FA. The increased acetyl-CoA levels allosterically inhibits citrate lyase enzyme and prevent the entry of acetyl -CoA into the cytoplasm. It is the cytoplasm where FA synthesis takes place.

c) Due to citrate synthase inhibition, the citrate produced is reduced in quantity. The substrate for FA synthesis, the acetyl- CoA, is reduced. Hence cytoplasmic levels of acetyl –CoA are low. To sum up, the reduced pyruvate reduces the kinetics of PC and slows the anaplerotic reaction involving citrate shuttle during conversion of OA into PEP. Consequently, the cytoplasmic acetyl -CoA is reduced. The low level of acetyl-CoA inhibits ACC, the consequences of which are reverse of expected de novo synthesis of FAs, i.e. stimulation of β -oxidation of fats. So, there is reason enough to believe that glucogenic FA synthesis suffer set back. The other way is lipid synthesis from exogenous and endogenous FFA by esterification of glycerol released from lypolysis or produced via HMP shunt. Experimentally verified facts suggest the substrate for acetyl- CoA in starvation is acetate, as seen above, which is insignificant under physiological conditions, when the de novo synthesis of FA predominates [9].

**Step 3:**

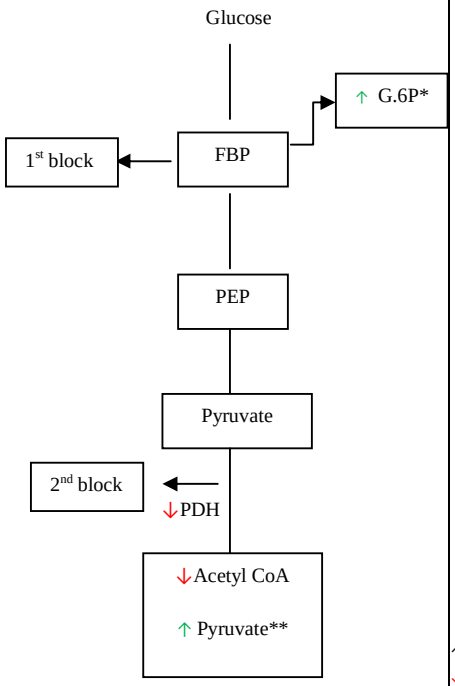
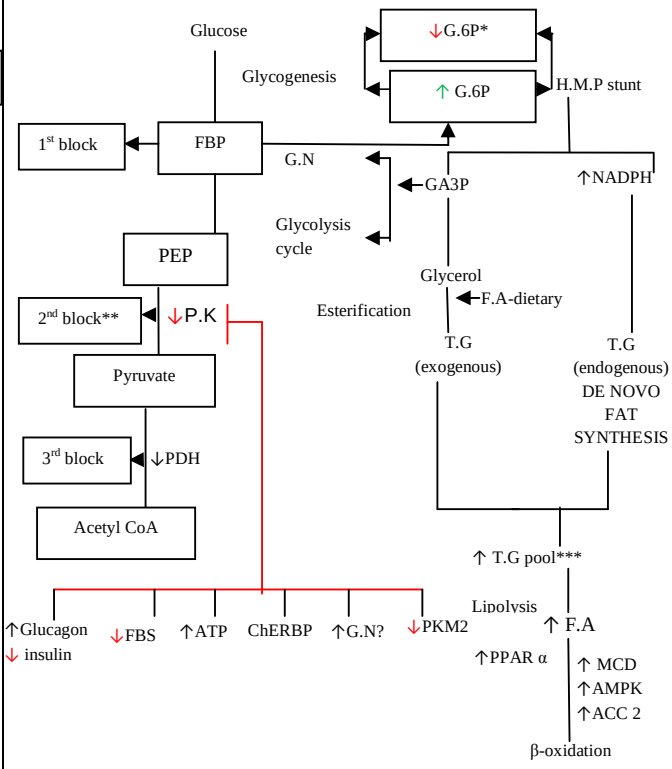
Re -activation of β -oxidation and its perpetuation:-

The cytoplasmic acetyl CoA and the NADPH, both being substrates for ACC in Conversion of pyruvate to malonyl –CoA by ACC, their reduced levels inhibit ACC. Malonyl-CoA is consequently reduced which leads to stimulation of β -oxidation. It may be noted that this stimulation of ACC is brought about independent of AMPK (by low acetyl CoA level inhibiting ACC) which continue to inhibit PDH. Thus while β -oxidation is restored, glycolysis is still under inhibition, initially by PDH and perpetuated later by PDK 4. Also the citrate produced thus partly removes the inhibition of ACC by AMPK, allosterically, through forward loop stimulation, which further augments the passage of β -oxidation products through the citric acid cycle [10]. On the other hand, the LCFA inhibit ACC through negative feedback regulation, through phosphodiesterasae induced inhibition of c AMP and PK, favoring β –oxidation [11]. At transcription level, ACC is regulated by SREBP I C through insulin and by ChREBP by high carbohydrate diet. Once the β - oxidation cycle starts, the GN stops. The GN pathway remains shut off until the end of β -oxidation cycle and cellular energy level indicators are high. When the cellular energy levels are high, β –oxidation is shut off by the inhibited AMPK, and simultaneously the GN begins. Thus the β -oxidation cycle and gluconeogenesis cycles alternate while glycolysis is inhibited. This explains the continuation and perpetuation of β -oxidation suppressing the glycolysis without there being any substrate competition, thus invalidating the substrate competition theory of Randle.

The cytoplasmic events (Table 3):-

Is Pyruvate level increased or decreased consequently to PDH inhibition? The answer to

**Table 3. Blockages of Glycolytic pathway in starvation/DM2**

| Randle cycle | Proposed hypothesis |
|---|---|
|  |  |
| **Only two blocks are suggested by Randle as seen above.**<br><br>*** Experimentally disproved subsequently.**<br>**** Pyruvate accumulates consequent to failure to enter TCA cycle due to inhibition of PDH.** | **An additional 3rd block at the level of PK is suggested by this hypothesis.**<br>*** Re-routing of increased G.6 P into glycogenesis pathway and HMP stunt explains the experimental observations of non – increased of G.6P.**<br>**** Proposed additional block.**<br>**-causing low Pyruvate level.**<br>***** Replenishes TG pool to allow perpetuation of β-oxidation indefinitely in untreated DM type 2.** |

this question is crucial for the proposed hypothesis, because as already seen above, β – oxidation he stimulation in post PDH inhibition is explained by low substrate {the pyruvate) decreasing the ACC activity (but not by stimulation of AMPK), Hence the pros and cons of increased or decreased pyruvate levels are examined in the light of available objective evidence.

Case 1 -Pyruvate level is increased: -

The block at the PDH level would lead to accumulation of pyruvate and lactate- both being gluconeogenic substrates [12]. Increased substrate would increase the rate of gluconeogenesis. Pyruvate, in excess of mitochondrial oxidation capacity (suggested by high acetyl CoA level) is carboxylated by PC and used by anaplerotic route to form cytoplasmic oxaloacetate (OA). Anaplerosis replenishes citric acid cycle intermediates [13]. The pyruvate is converted to oxaloacetate in the mitochondria which is brought into cytosol by means of citrate / malate shuttle, (as oxaloacetate in the mitochondrial matrix, cannot cross the mitochondrial membrane into the cytosol, which

is the site of gluconeogenesis and de novo lipogenesis). Since In starvation the reducing equivalent, NADH level is low, the citrate shuttle is preferred to raise the concentration of the later. So, OA is converted to citrate which freely diffuses into cytosol and is split into OA and acetyl CoA by citrate lyate. Thus with every molecule of citrate that enters the cytosol, there is a corresponding increase in acetyl -CoA in the cytosol. If gluconeogenesis is augmented, due to increased pyruvate, (case 1), the acetyl –CoA level in cytosol should also increase. Consequently the ACC followed by malonyl -CoA are stimulated by the increased acetyl-CoA. The result is increased lipogenesis, as Inhibition of CPT 1 due to increased malonyl -CoA leads to inhibition of β- oxidation. But this is just opposite of what Randle cycle proposed i.e. increased β - oxidation of fats. So it is unlikely that the pyruvate level will be increased consequent to the inhibition of PDH.

Case 2:- Pyruvate level is decreased.

Interestingly, the decreased Level of pyruvate would lead the events in the direction of increased β oxidation, as conceived by Randle cycle. Hence it is suggested that the pyruvate levels might be low. The second block which is proposed, after PFK and before pyruvate formation would also cause low pyruvate levels. This would be possible if the block occurred at the level of PK. This would result in decreased production of pyruvate which would lead the subsequent events in the direction conceived by Randle for increased β-oxidation.

Objective evidence in favor of low pyruvate level:-

a) Under the conditions of increased glucagon/insulin ratio, the PK is inhibited by glucagon, phosphorylating Pyruvate Kinase (PK) through Pyruvate Kinase A (PKA) and insulin lack failing to dephosphorylate through PK Phosphatase.
b) The increased level of ATP (due to increased fat oxidation) further inhibits the PK by negative feedback inhibition. Of all the regulators of PK i.e. the hormonal (glucagon, epinephrine and insulin) the covalent and allosteric effectors (FBP, ATP), the allosteric feed forward stimulation by FBP is considered important while others are considered secondary. [14] FBP is reduced due to inhibition of PFK 1 which converts F-6P to FBP; the allosteric stimulation by FBP is reduced leading to reduced stimulation of PK.
c) In DM2 rat's chronic stimulation of pancreatic β -cells by glucose due to increased peripheral resistance of insulin decreased PK activity and pyruvate cycle [15]. When cellular glucose levels are high, it signals stoppage of anabolic GN process and stimulates catabolic glycolysis .This keeps PK active. But when cellular glucose is low (due to peripheral insulin resistance), GN is stimulated and catabolic glycolysis is shut off.
d) c AMP binds to ser196 and thr 666 sites of ChREBP, causing phosphorylation and inactivation of PK by stimulating Protein kinase A (PKA) .Glucagon which is increased in DM2 increases the level of c AMP to initiate the reaction.
e) An analogy between cancer cell physiology and DM2 is suggested. The PK M2 in its inactive dimeric isoform, in response to increased reactive oxygen species (ROS) production in lungs by cancer cells diverts glycolytic flux from glycolytic pathway to HMP shunt with consequent production of NADPH, which prevents oxidative decay in lungs by increased ROS. However, though PK M2 expression in tumors is seen, such effect in DM2 and allied condition producing increased ROS has not yet been shown. But there are some redeeming facts like hypoxia which produces ROS through complex 3 of Electron Transport Chain (ETC) also inhibit PK M2. In DM2, due to increased β–oxidation is increased ROS production from complex 3. Further FBS, through forward loop stimulation activates PKM2 promoting PEP conversion to pyruvate. On the other hand, reduced FBS inactivates PKM2 to its dimeric form when the flux is routed through HMP shunt. The FBP is low in DM2, and there is no reason why the inhibition of M2 and channeling through HMP shunt should not occur. Another fact is that at transcription level inter -conversion of M1 (mostly expressed in all tissue ETC and M2 isoforms, (which is known to be expressed in embryonic tissues and rapidly dividing cells/cancer cells). Thus the role of PKM2 is crucial as it can explain everything including blocking of glycolysis, opening of HMP shunt / GN pathway and the preponderance of β - oxidation of fats as an alternate source of energy metabolism.

Future research may elucidate the potential role of PKM2 in DM2.

The net effect is reduced / non-conversion of PEP to pyruvate. The blocking of glycolysis at various steps under conditions of fasting/ starvation makes the pyruvate level low. Reduced level of pyruvate is linked to reduced ACC and MCD (see below)which increase the β-oxidation of fats while glycolysis is under inhibition by PDK4 (whose expression is increased in fating / starvation) by its indifference to change in pyruvate levels. PDK expression is increased in starvation and D2M which keeps PDH inhibited [16]. Also PDK4 which is highly expressed in starvation, by its indifference to pyruvate, keeps PDH under inhibition [17].

The HMP shunt: -

It is suggested already that when fat supply, fuelling the β – oxidation in starvation is exhausted as in starvation, say by 40 days or so of fasting the person dies where as even untreated, DM2 pts survive for years even without treatment, implying that fat sores are replenished to provide fuel for the continued β – oxidation It is proposed for the first time that this is achieved by bringing HMP shunt as a compensatory measure by the body in DM2.In spite of block at the level PFK, why Glucose 6 Phosphate (G6P) has not increased on experimental verification is because the increased G6 P is routed through glycogenesis and HMP shunt. This explains the increased glycogenesis seen in fasting, exercise, as well as in DM2 [18]. The following facts make HMP shunt operational.

a) Increased availability of the substrate (G-6P) consequent to block at the PFK level by stimulating Glucose 6 Phosphate dehydrogenase (G-6 PDH), opens the HMP shunt. The enzyme is in an equilibrium state between T state and R state. Allosteric inhibitors tilt the equilibrium to T (inactive) state and increased concentration of the substrate tilts back the enzyme to R (active) state. The stimulatory effect of increased substrate balances the allosteric inhibition of the enzyme [19].
b) Under the physiological conditions, the rate limiting enzyme G-6 PDH would be in inhibitory state due to the increased ratio of NADPH /NADP. As the NADPH/ NADP ratio decreased, due to increased β -oxidation, and consequent reactive oxygen species (ROS) production, the inhibitory effect on G-6PDH would be lifted and the shunt starts operating.
c) Initiation of HMP shunt is also because of the increased demand for the reducing equivalents- the NADPH, as β-oxidation of fats generates increased ROS production as seen above, which needed to be scavenged [20].
d) NADPH is needed for conversion of acetyl Co A into malonyl CoA, for de novo synthesis of FA.
e). If the perpetuation of oxidation of fats were to continue, the need for continuous supply of the substrate (fats) for lypolysis is imperative and HMP shunt fulfills this obligation. As the name indicates, the shunt is an alternate pathway to reestablish the continuity of glycolytic pathway, especially when there is a block ahead (as in this case FBP) and hence expected to be functional. Through the end products, glyceroldehyde-3-phosphate (G3P) and F-6P it can enter the synthetic pathway–lipogenesis, or GN path way, or may continue glycolytic pathway to produce pyruvate.
f) Its role in functioning along with inhibited PKM2 in diverting the glycolytic flux is already seen above.

DM2 reinterpreted in terms of Randle cycle:-

Randle cycle was described originally in the context of fasting and fed states as well as during exercise - all being physiological states. Later it has come to be applied to DM2 and Insulin Resistance (IR) – both being pathological conditions. DM2 being initiated by insulin resistance (IR) which is due to hyper insulinemia / insulin lack, was a problem due to ineffective insulin action. In starvation the initiating factor is high levels of glucagon which is highly expressed in conditions like starvation etc. Death is certain in starvation if re-feeding is not being started, sooner or later. In DM2 even if untreated the survival time will not be as short as starvation. This may be because of the balance struck between lipogenesis (probably through operation of HMP shunt, as proposed) and β -oxidation. No involment of HMP shunt is reported in Randle cycle till date. Probably such compensatory mechanisms may not be operational because of shorter survival time as in the case of fasting. It is felt that caution needed to be exercised in

stretching any further the analogy between the physiological state of fasting and DM2. Hence it is felt necessary to 'spruce the basement (the Randle cycle) before dusting the superstructure' (DM2). As could be seen the alternate mechanism proposed by the present hypothesis can be adopted as to explain how β – oxidation over rides glucose oxidation in DM2 without invoking IR as a primary event thus resolving the perpetual dilemma as to whether insulin resistance is primary event or secondary to switch over of energy metabolism to B-oxidation. The increased glucagon/ insulin ratio is enough to explain the above mentioned switch of energy metabolism and once the process starts it is self perpetuating in DM2. Unlike in other situations considered by Randle, the increased glucagon/ insulin ratio is reversed by feeding or re -feeding as in inter-pranidial state and fasting respectively, resulting in β -oxidation and glucose oxidation alternating one another, in DM2 once β -oxidation overtakes glucose oxidation, because of insulin resistance there is no reversal to glucose oxidation. Thus a perpetual preponderance of b-oxidation in DM2 occurs, unless intervened by exogenously administered insulin supplemented. Further as events in liver and cellular level are more relevant in whole body management of energy metabolism than muscle, whose energy metabolism caters to the requirements of muscle itself rather than body in general, the events depicted in this article are more related to the former than later.

Further proof in favor of the proposed hypothesis: -

It is accepted that in DM2, metformin is effective in reducing the fasting hyperglycemia by stimulation of AMPK which results in inhibition of gluconeogenesis. It is imperative therefore that AMPK is in inhibited condition in DM2. The proposed hypothesis also emphasizes that AMPK is inhibited and the stimulation of n is not through stimulation of AMPK but low substrate, pyruvate reducing ACC which in turn reduces Melanoyl CoA ,the later by stimulating CPT1 stimulates β – oxidation.

Therapeutic implications:-

Since the events start from the inhibition of PK in DM2, leading on to the chain of subsequent events i.e. low pyruvate level- low cytoplasmic acetyl-CoA-low ACC-low melanoyl- CoA-CPT 1 stimulation-induction of β – oxidation, stimulation of PK by a suitable pharmacological agent may reverse the events in favor r of glucose oxidation. The stimulated PK may not only augment glycolysis but may also check PEP- CK and inhibit GN, leading to reduced fasting hyperglycemia.

## 2. IMPLICATIONS FOR FUTURE RESEARCH

Since it is seen that PKM2 controls, whether the glycolytic flux is to be continued to pyruvate production by stimulating PK, or through GN pathway by inhibiting the PK, as seen in case of tumor metabolism, PKM2 may hold a key to the pathogenesis, treatment of DM2 also. In this regard, drugs those stimulate the PKM2 need to be evaluated. Future research, in this direction may be fruitful, it is hoped.

Testing the hypothesis:-

1) Measure the activity of the enzymes PK, ACC, and melanoyl CoA. Their low activity is in support of the hypothesis. Measure the activity of G6PDH. High activity is suggestive that HMP shunt is operating.
2) Measure the levels of pyruvate and cytoplasmic acetyl CoA. Low levels support the hypothesis.
3) Testing the status of PKM2, weather stimulated or inhibited in DM2.

## COMPETING INTERESTS

Author has declared that no competing interests exist.

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