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Elevated System Energy Expenditure in Sickle Cell Anemia

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1. Introduction

In Sickle-cell Anemia (SCA), anergy (lack of metabolic energy) and elevated resting energy expenditure (REE) are commonly observed phenomena. The many systemic changes in Sickle-cell anemia are, therefore, associated with measurable changes in patterns of energy uptake, utilization and efficiency. Understanding the scientific basis of these structural and energy changes suggest mechanisms of possible amelioration.The structural and energy changes in sickle-cell anemia can be viewed at different levels: at the level of the whole person, as reflected in anergy and elevated resting energy expenditure. At the level of the whole blood tissue, as shown in lowered blood pH (high hydrogen ion, H^+, concentration). This is also associated with structural changes in polyhedral charge-packing of hydrogen and hydroxyl ions (octahedral charge-packing, which is the ideal is not achieved). At the specific organ level, this is shown in the elevated energy cost of kidney proton-dialysis. Because of this kidney disease is a major cause of death among sickle cell sufferers. The cellular level shows the disruption of the erythrocyte membrane itself. The anti-turbulence biconcave 'erythrocytoid' shape is changed to the sickle-shape, resulting to increased blood flow-turbulence. This overworks the heart; causing high heart disease rates among patients. At the molecular level, this results to, for example, the inability to metabolize the key energy-source molecule glucose. This results to, as well as inability to extract energy from glucose, glycation of hemoglobin. Glycated hemoglobin has poor oxygen-carrying power, compounding the problem of the little hemoglobin available. Also there are shifts in redox equilibriums, enzyme and metabolite concentrations and activities, and so on. All these result to extra-energy costs to try to restore system optimal state of efficiency and stability. All these, together, explain elevated resting energy expenditure in sickle cell disease.

Different researchers have, over the years, discovered that sufferers from sickle cell anemia (SCA) expend more energy maintaining the same mass of their bodies than normal people (Kopp-Hollihan *et al*, 1999; Borrel *et al,* 1998). Some have worked to establish more efficient measurements of the observed differences from normal (Buchowski *et al*, 2002). Others have worked on theories and experiments towards remediation (Bourre, 2006; Enwonwu, 1988). On the internet, there are sites actively publicizing high-energy foods they consider ideal for sickle cell sufferers (Sherry, 2011). In folk medicine in the African communities, where sickle anemia is common, easy to digest high-energy foods are usually recommended for sickle cell patients.

To appreciate why a sick body, such as that of the sufferers of sickle-cell anemia, would cost more energy to maintain, as reflected in the higher resting energy expenditure (REE), than

normal people's, we have to, first, appreciate some simple rules, with respect to energy economy; that nature employs in the design of natural systems. The living system, including the human body, is the ideal natural energy-using system. The living system is energy-conservative; efficient, compared to any other known system, in nature.

The rule is that for a given system in nature there is a functionally ideal arrangement. This ideal or optimal (not perfect, but best possible) arrangement is most energy efficient. It offers the best stability (*stay-ability*) to the system. The human body is designed to operate at optimal conditions; where it is most bio-energetically efficient and stable. Stability in human terms means good health, less stress and pain, and long life. Sickness, generally, is a state of body-system displacement from the optimal conditions of function and is, therefore, energy costly. The fever (abnormally high body temperature) commonly associated with sick people results from the decrease in efficiency of body energy use.We recall that entropy, disorderly flow of system energy, increases with temperature. Such elevated basal body temperature (high metabolic entropy) is commonly found in sickle-cell anemia sufferers, particularly during crisis.

The following statement by the researcher Zora Rogers (2011) "Fever is a common presenting symptom in many manifestations of sickle cell disease" summarizes the situation. Heat loss (fever) is sign of wasting energy. That is why the sufferer, inspite of higher *Resting Metabolic Energy* (RME) utilization, suffers from anergy (a state of lack of energy). Much of the energy and nutrients, including ascorbic acid, the reducing metabolite glutathione, etc, consumed or produced by patients of this disease are wasted (Fakhri *et al*, 1991; Kiessling *et al*, 2000; Reid *et al*, 2006). They go into the dissipative chaos of entropy, instead of being organized as parts of stable system structures such as fat, healthy nerves and muscles, which SCA sufferers lack. In this sense sickle cell anemia is, literally, a wasting disease. Energy and structures are dissipated.

2. Some contributing factors to energy wastage in sickle cell anemia (SCA)

There are so many factors that contribute to systemic energy wastage in sickle cell anemia. Because of its dramatic manifestations as anemia, particularly during crisis, sickle cell disease is seen, primarily as an anemia. The catastrophic fall in red blood cell concentration; and the accompanying yellow eyes, caused by excess bilirubin (a by-product of hemoglobin breakdown) would easily identify the disease as of blood origin. This assumption is sustained by the direct link between hemoglobin and blood oxygen concentration on the one hand and body energy generation on the other. Anemia can, therefore, be thought of, equally, as low energy metabolism syndrome; and more so for a chronic condition like sickle cell anemia. The first major factor that leads to anergy in sickle cell anemia is inefficient glucose metabolism.

2.1 Inefficient glucose metabolism in sickle cell anemia

Glucose is the main fuel molecule of the human body. Some key body cells depend mostly or solely on glucose for energy metabolism. Two of these glucose-dependent body cells include the red blood cell (rbc) and nerve cells, including brain cells. It is clear that anybody in whose body system glucose metabolism is compromised is in trouble with the vital tissues and organs associated with these cells; blood system and nervous system. This happens to be the case in sickle cell anemia. In SCA hexose metabolism is deranged

(Osuagwu and Mbeyi, 2007). Table 1 below shows the consistent rise in blood glucose level from the normal genotype (HbAA), through the one-gene (HbAS) and double gene-dose (HbSS) to the crisis (HbSS-crisis) state. The diminishing capacity to utilize glucose is seen to be, inadequately, compensated by the consistently enhanced utilization of extra fructose, from one state to the other.The differences are statistically significant between the states (Osuagwu and Mbeyi, 2007). This implies that the issue of capacity to utilize glucose should, by itself, be considered seriously, in handling anemia cases. Part of the explanation for this is that glucose is activated with the high energy molecule adenosine-triphosphate (ATP) by phosphorylation, before it can go into a cell. In a person with anergy (lack of metabolic energy), such as SCA patients, there is a shortage of the ATP to phosphorylate glucose. Fructose that gets into cells by passive transport or facilitated diffusion is consumed, in partial compensation. Exhaustive depletion of fructose in SCA should, by itself, be of primary concern. This is because the basic metabolism of cells that depend mainly on fructose, such as spermatozoa, would be compromised in the sickle cell disease state. This could be a major explanation for the poor spermatozoa health; and infertility observed in sickle cell males. The number, motility and other indices of spermatozoa vitality are all poor in men with SCA (Osegbe et al, 1981).

Any measure to promote glucose uptake into the cell would be of much help to SCA sufferers. Administration of insulin to facilitate glucose uptake for sickle cell sufferers in crisis is a management measure that logically suggests itself.This should be systematically investigated. By facilitating trans-membrane glucose transport, this measure will also result to better fructose conservation; and better sperm health and fertility. This should help sickle cell males live better lives; and bear healthier children.

Sickle Cell State	Number of Subjects In Group	Plasma Glucose Level, mg/dl	Plasma Fructose Level, mg/dl
HbAA	35	70.10 ± 7.50	1.32 ± 0.08
HbAS	32	74.75 ± 6.20	1.25 ± 0.05
HbSS	34	78.59 ± 4.20	1.09 ± 0.05
HbSSc	33	84.80 ± 4.10	0.99 0.04

Table 1. Plasma Glucose and Fructose Levels in Sickle Cell States.

2.2 Deranged pyruvate metabolism

Another major cause of poor glucose metabolism in sickle cell anemia is the non-efficient utilization of the end product of glycolysis; pyruvate. Table 2 summarizes this condition. The critical step in the generation of most energy (ATP) and reducing power (NADH) for the whole system fails in sickle cell disease; See Fig 1. Fig1, Fig 2 and Table 2 help to explain both anergy and acidosis in sickle cell anemia.

Sickle Cell State	HbAA	HbAS	HbSS	HbSS-crisis
Lactate Level, mM-L^{-1}	0.74 ± 0.19	0.75 ± 0.23	27.60 ± 1.39	31.40 ± 2.56
Lactate ratio	1.00	1.01	37.30	42.43
Pyruvate Level, mM-L^{-1}	0.11 ± 0.02	0.11 ± 0.03	2.03 ± 0.05	2.08 ± 0.11
Pyruvate ratio	1.00	1.00	18.45	18.91
Lactate/pyruvate	7.01	7.02	13.60	15.07

Table 2. Lactate and pyruvate levels in different sickle cell states.

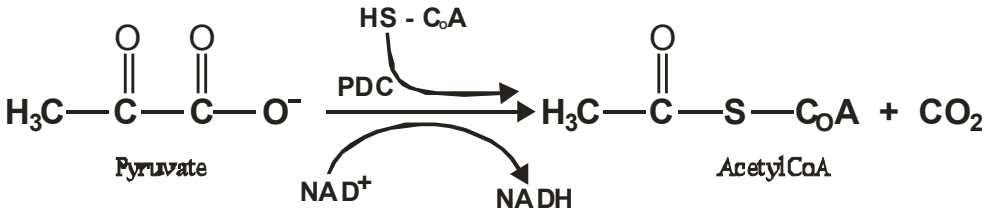

Fig. 1. Pyruvate dehydrogenase complex (PDC) links glycolysis to tissue respiration.

Pyruvate is the end-product of glycolysis and feedstock material for the production of Acetyl-CoA for the TCA cycle. If acetyl-CoA, the gate-substrate of the tricarboxylic acid (TCA) cycle is not generated, by successful pyruvate conversion, then most of the free energy stored in glucose cannot be extracted. This would, and does, result to anergy.

If reduced nicotinamide adenine dinucleotide (NADH) is not generated, there would be insufficient reducing power for the body system, down the electron transport chain; hyper-oxidation, excess free radicals, etc., will result. There is indeed observed hyper-oxidation and excess free radicals found in the body system of sickle cell patients, as theory indicated.

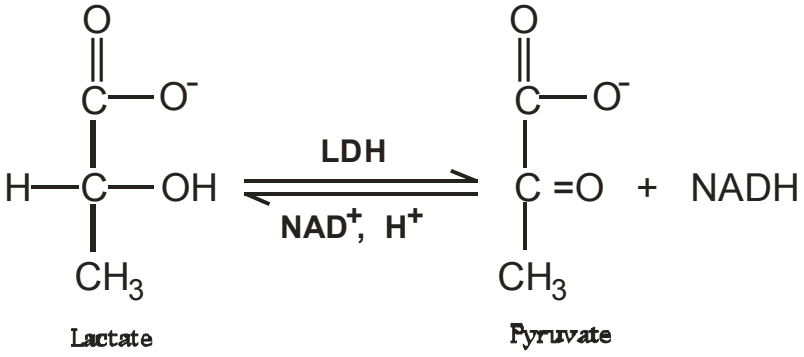

Fig. 2. Reversible oxidation of lactate to pyruvate.

If pyruvate accumulates, the equilibrium of Fig 2, which naturally favours the generation of lactate from pyruvate (Murray et al, 2006), will result to what is displayed in Table 2; a higher and higher ratio of lactate to pyruvate. Lactate acidosis will be the end result as observed in sickle cell patients. See Table 3. The data of Table 2 also best explains the dramatically different existential outcomes for single gene carriers (HbAS) as compared to double dose carriers (HbSS). The expression of the Sickle cell gene in relation to the pyruvate dehydrogenase complex is sigmoid (Osuagwu, 2009). Both the HbAA and HbAS values fall around the same point; which is why the HbAS, trait-carrier group, do not manifest the proportionate impact of the disease, as expected from theory. This suggests that the system-equilibrium mechanism of the HbAS is much better preserved than theory would suggest. But there is still an energy cost. The HbAS are not a hundred percent free of the pathological manifestation of the gene, as the popular notion suggests. They pay a smaller than expected energy price.

2.3 Energy cost of acidosis in SCA

A look at Fig 3 tells a simple story; the human body was designed by nature to be, overall, alkaline. The human body is by design an electron-rich system (alkaline). Food is a neutral substance that the human body can absorb, extract electrons (mostly as H· attached NAD^+; NADH, etc) from. It then safely excretes the associated positive charges, particularly hydrogen ion, H^+. As Fig 3 shows all the major body fluids are alkaline (electron-rich); all the excretory body fluids are acidic (hydrogen-ion rich).Part of the reason for this alkaline design is body energy economics. It is more efficient to extract energy from energy-rich molecules in an alkaline medium.

Consider the hydrolysis reaction that extracts energy from the key energy currency of the body adenosine triphosphate, ATP:

$$ATP^{4-} + H_2O \rightleftharpoons ADP^{3-} + HPO_4^{2-} + H^+ + \text{Energy}$$

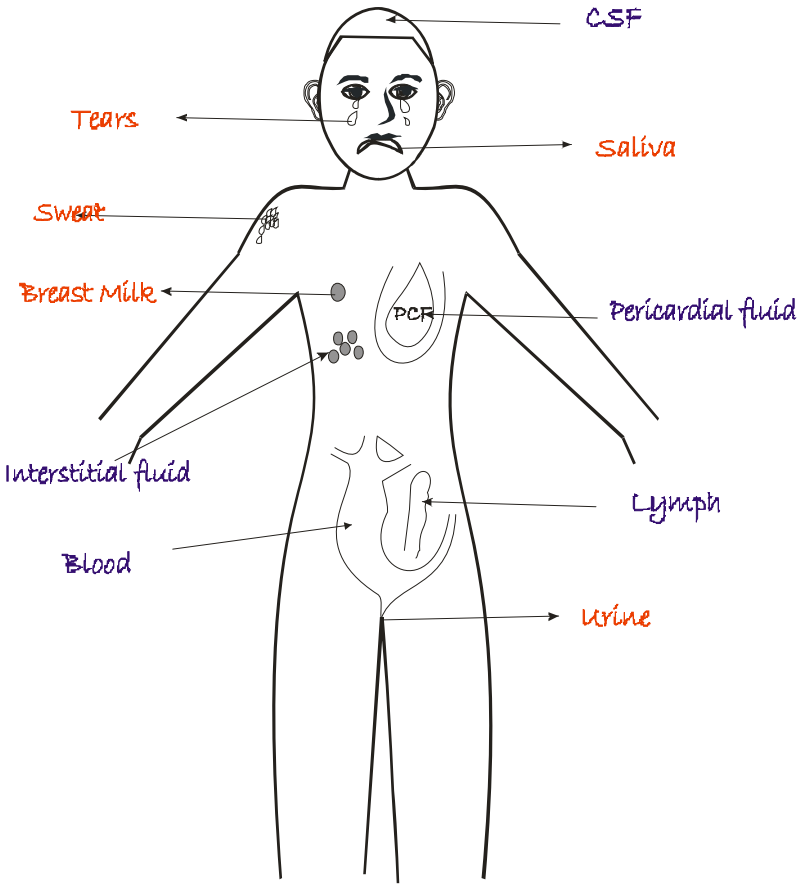

Fig. 3. Human Body Fluids in pH Color Codes.
Internal Body fluids are alkaline (blue); excretions are acidic (red); CSF = cerebro-spinal fluid.

A product of this reaction is the hydrogen ion, H^+, which gives acids their character. Le Chatellier's principle, on the self-restoring tendency of displaced equilibrium systems, teaches that ATP hydrolysis in acid medium would be resisted, because one of the products is an acid, H^+. To push ATP hydrolysis under such condition would in itself cost energy. In addition, the efficiency of the ATP hydrolyzing enzyme, ATPase, decreases with increasing acidity (Bronk, 1973). We know enzymes are denatured by acids, outside normal range of function. This implies extra energy cost and waste. On the other hand ATP hydrolysis would proceed rapidly in a more alkaline medium that would consume the produced H^+. The more alkaline the better; within physiological range. ATP hydrolysis is more efficient, yields more energy, in more alkaline medium (Manchester, 1980).
In recent times, there have been groups or movements, particularly via the internet, promoting the '*Alkaline Body*' as the ideal body. Their arguments are based on some of the points noted here. The problem with their position is they don't seem to realize that excess alkalinity of the body (alkalosis) is in itself a disease. The body is designed on the optimality principle. And human survival at beyond pH 7.65 is difficult.

2.4 Low blood pH in SCA

Table 3 shows clear tendency towards more acid body fluid, as the sickle-gene dose/state increases.Therefore the sickle cell sufferer's body consumes more ATP to do the same amount of, say, muscular work. The energy cost of extracting the same amounts of hydrogen ion, H^+, from blood into urine illustrates this point well. This data agrees with the theory outlined above.The more energy exerted to do the same amount of work, the more stress would be associated with it.

S/No	Genotype/State	n	Blood pH,	Urine pH,
1	HbAA = 0	42	7.39 ± 0.07	6.54 ± 0.15
2	HbAS = 1	42	7.35 ± 0.09	6.44 ± 3.15
3	HbSS = 2	42	7.32 ± 0.08	5.89 ± 0.39
4	HbSS-crisis = 3	42	7.15 ± 0.12	4.75 ± 0.46

Table 3. Sickle State, Blood and Urine pH.

2.4.1 Energy cost of kidney hydrogen ion dialysis in SCA

From the data of Table 3, the estimated enthalpies of dialysis, ΔH_d, for each of the four states are: HbAA = 1.96RT; HbAS = 2.10RT; HBSS = 3.29RT; HbSS-crisis = 5.53RT. The estimated entropies of dialysis $T\Delta S_d$, compared to the normal HbAA state are: HbAA = 0.00RT; HbAS = 0.14RT; HbSS = 1.34RT and HbSS-crisis = 3.57RT ($R = 8.31 Jmol^{-1} K^{-1}$ and $T = 303K$). This offers a bio-energetic explanation of why the kidney of the sickle cell disease sufferer, on average, fails at an early age; and is the top source of morbidity (Saborio and Scheinman, 1999; Osuagwu, 2007). The kidney hydrogen, H^+, dialysis energy expenditure gap between SCA sufferers and normal is so wide that it is somewhat surprising.

S/No	Genotype/State	n	ΔH_d	$T\Delta S_d$
1	HbAA = 0	42	1.96RT	0.00RT
2	HbAS = 1	42	2.10RT	0.14RT
3	HbSS = 2	42	3.29RT	1.34RT
4	HbSS-crisis = 3	42	5.53RT	3.57RT

Table 4. Indices of Energy Cost of KidneyHydrogen Ion DialysisIn SCA.

This data confirms that the stress, in this specific case of kidney proton dialysis, suffered by the HbAS individuals (7% more) compared HbSS-steady-state (68% more) and HbSS-crisis (182% more) for doing the same amount of system work compared to the HbAA, non-carrier individuals are high. In the specific case of HbSS-crisis, three times normal. This, among others, explains why resting energy expenditure of the SCA sufferer is high. This phenomenon, of disproportionate severity of gene expression in genotypic disease conditions, is likely to be observed in varying amounts in other genetic diseases. The explanation is likely due to interaction with other genes, which help buffer the effect of the defective gene. Also noteworthy is the general fact that a complex system under stress tends to self-conserve; and does so better the closer it is to ideal state, as HbAS is compared to HbSS. Any SCA anemia management measure that reduces hydrogen ion accumulation, or that can provide an alternative route for its excretion would be of major relief to the patient.

2.5 Energy cost of change in blood system charge-parking arrangement

Nature, always, prefers the optimal structure and associated energy expenditure in designs of system. One of these choices for optimality is in the packing of charges in living things (Osuagwu, 2010). The pH values we are familiar with represent ratios of hydrogen ions, H^+, and hydroxyl ions, OH^-, that can be packed together, with optimal stability.

Comparing the concentrations of hydroxyl and hydrogen ions in the bloods of normal (HbAA) and sickle sufferers at their measured pHs from Table 3 above reveals the data of Table 5. Similar charges repel and opposite charges attract each other. The most efficient way to arrange six hydroxyl ions to one hydrogen ion in the normal, HbAA, blood (pH = 7.39) would be as octahedron; the most efficient way to arrange four to one in HbSS blood (pH = 7.32) would be as tetrahedron (Fuller, 1975). The octahedral arrangement is the optimal considering, jointly, energy efficiency and stability. Any shift from this ideal is less efficient; and energy costly. This is one other way sickle cell sufferers pay a higher energy cost to try to maintain their body system. The stress wears their system down with time, faster than for normal people.

It has been noted that, generally, any shift from the ideal charge-packing arrangement would result to sickness (Osuagwu, 2007). Larger hydroxyl to hydrogen ratios, such as found in alkalosis is also troublesome; and disease-causing. The pH 7.65, which affords a hydroxyl to hydrogen ion ratio of 20: 1, is consistent with packing on the twenty vertices of the dodecahedron with the lone hydrogen ion at the centre of the structure, held in place by weak coordinate bonds to the surrounding hydroxyl ions. 20: 1 is the largest ratio consistent with life. Beyond that, death occurs.

GENOTYPE	HbAA	HbSS
PARAMETER		
pH	7.39	7.32
$[H^+]$, mol-L^{-1}	$10^{-7.39}$	$10^{-7.32}$
pOH	6.61	6.68
$[OH^-]$, mol-L^{-1}	$10^{-6.61}$	$10^{-6.68}$
$[OH^-]/[H^+]$	$6.03 \approx 6$	$4.37 \approx 4$
Efficient –packing Structure	Octahedron	Tetrahedron

Table 5. Hydroxyl to Hydrogen ion Concentrations and Ratios Represented by Measured pH.

2.6 Energy cost of stresses on the erythrocyte

The red blood cell, erythrocyte, whose structural and physical collapse, sickling, has given the name to SCA is of special interest in accounting for the high energy expenditure in the disease state. Sickling, erythrocyte structural collapse, occurs because the cell is overwhelmed by stresses. Two such stresses are:

2.6.1 Erythrocyte and failure of glucose metabolism in SCA

What happens to a cell that depends solely on glucose if its metabolism fails? From significant data, some presented here, and published work (Osuagwu and Mbeyi, 2007), glucose metabolism is subnormal in SCA. But the erythrocyte, like the nerve cell, depends mostly on glucose for energy. SCA erythrocyte lacks the energy to maintain the integrity of its cell membrane (Osuagwu et al, 2008). This is a significant reason for SCA erythrocyte instability.

2.6.2 Excessive oxidative stress

An acidic medium is an oxidizing medium. The proton, H^+, is nature's unit oxidant. The acidic sickle cell sufferer's body-fluid, such as blood is, therefore, inherently oxidizing. Red blood cell that is embedded in this oxidizing medium, in this case the blood stream, becomes a victim. Its lipid, electron-rich membrane is oxidized; becomes rigid and breaks down.

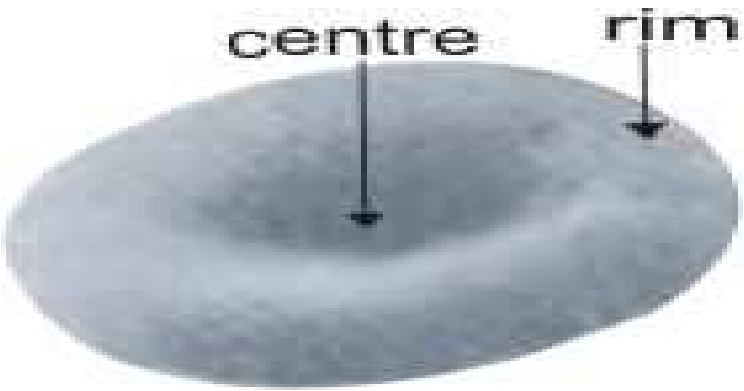

Fig. 4. Dimensions of the erythrocyte; ratios are powers of pi (3.14...).

The dimensions of the erythrocyte (Centre thickness: rim thickness: diameter: circumference) are fractal, sequential, powers of pi ($\pi = 3.14...$). This is the origin of the pi-discoid shape of the erythrocyte (Osuagwu, 2007).This pi-biconcave shape locates the greater part of the mass of the cell at the rim. This results to a very large moment of

inertia; low angular momentum and great resistance to turbulence (Uzoigwe, 2006). This 'erthrocytoid' shape is the best to minimize frictional breakdown of the erythrocyte in the very viscid blood stream, through which it is propelled at great blood pressure, and speed, by the heart.Oxidative damage, by contributing to sickling, destroys this energy efficient pi-biconcave structure; increasing energy cost of blood-stream transport; and energy cost of forming new cells, with a rapid bone-marrow turnover. This is why sickle cell anemia also involves cardiovascular problems (Serjeant, 1974). Studies show that movement across the cell membrane is deranged; and the ion pumps that help maintain the trans-membrane concentration gradients consistent with life are compromised (see Table 6). It is observed that the concentration gradients of these cations deviate from the normal as the sickle condition intensifies.

Measure	**HbAA**	**HbAS**	**HbSS**	**HbSS-c**
No. of Subjects	62	62	62	62
Na^+, out, mmol/L	139.59 ± 2.89	139.05 ± 2.73	133.74 ± 2.44	109.02 ± 1.93
Na^+, in, mmol/L	15.42 ± 2.48	19.03 ± 3.25	20.64 ± 2.51	28.20 ± 1.69
K_{eq}-Na^+(out/in)	9.0525	7.3069	6.4797	3.8660
K^+, out, mmol/L	3.51 ± 0.33	4.05 ± 0.39	4.72 ± 0.42	5.52 ± 0.48
K^+, in, mmol/L	103.35 ± 4.49	97.91 ± 3.86	88.08 ± 3.80	83.94 ± 3.56
K_{eq}-K^+(in/out)	29.4444	24.1753	18.6610	15.2065
Ca^{2+}, out, mmol/L	8.48 ± 0.42	8.04 ± 0.11	7.90 ± 0.21	5.06 ± 0.32
Ca^{2+} , in, mmol/L	0.46 ± 0.09	0.58 ± 0.08	0.60 ± 0.70	2.30 ± 0.32
K_{eq}-Ca^+(out/in)	18.4348	13.8621	13.1667	2.2000

Table 6. Trans-membrane Cation Concentrations and Gradients, Keq, in Different Sickle cell States.

If the concentration of the potassium ions, K^+, which is more representative of the potential across the membrane, is looked at; it is observed that the energy to maintain the cell membrane integrity decreases as the sickle cell gene dosage increases. There is consistent drop in system-maintaining energy; as shown across the cell membrane.

Measure	**HbAA**	**HbAS**	**HbSS**	**HbSS-c**
No. subjects	62	62	62	62
Keq	29.44	24.18	18.66	15.21
$\Delta H_{p,}$ K^+; J	8362.55±35.00	7988.33±253.66	7274.03±229.12	6952.29±211.49
Ratio	1.00	0.96	0.87	0.83

Table 7. Energy Decrease Across Cell Membrane as Sickle Cell Intensity Increases.

Because of this extra need for energy, the need for extra nutrients by the sickle cell sufferer has been known for a long time (Reed *et al*, 1987).

3. System energy wastage and sickle cell anemia management

The different points of energy wastage (high entropy) in sickle cell anemia, outlined above, have helped to explain the anergy (system lack of energy), instability and other symptoms

of the disease. They also offer clues as to points and modes of possible intervention for disease management. They also offer the possibility of rationalizing existing interventions that appear effective. Inability to extract reducing power/hyper-oxidation from nutrients; the build-up of glucose, acidosis, the viscid blood and erythrocyte lysis, etc., are all issues that can be dealt with by rational intervention.

Diet or nutritional management is already well-established as a method of sickle cell disease management. But from the facts outlined here, one can see that intervention to improve glucose metabolism would be very helpful to the SCA patients. Also would dietary supplements that promote pyruvate metabolism; such as lipoic acid. Alkalinizing nutrients would be of overall good. But acid-forming nutrients would need to be taken with care; as are agents that support free-radical generation and propagation.

Special care would have to be taken in relation to the impact of any management strategy on the kidney. As observed the organ is under severe energy stress in the sickle cell patients' system.We learn from Fig 3 that sweat-inducing exercises would do some good to the SCA patients, as part of the excess acidity will be excreted that way; taken care not to over-do it and induce crisis.

Overall, the observed elevation in resting energy expenditure (REE) by the sickle cell disease sufferer can be understood in terms of known energy-related physiological, anatomical and biochemical processes. They can, therefore, be managed, for amelioration, from the careful consideration of these.

4. Summary

The observed elevation of basal energy expenditure in sickle cell anemia has been explained, in this work, in terms of established principles' of nature and bioenergetics. The genetic programme that results to sickle cell anemia appears to involve more than the genes coding for hemoglobin formation; and bone marrow metabolism. Energy metabolism is, critically, involved. And the derangements along the energy pathways have consequences that affect different levels of system function and integrity. It is shown that management of sickle cell anemia by intervention along the body's energy metabolism pathways can be helpful, in relieving the anergy (lack of energy) experienced by the sufferers of the disease. This can come about, for instance, by stabilizing erythrocyte cell membrane; minimizing blood turbulence, cell lysis and enhancing oxygen carrying capacity. The consumption of foods or supplements that supply reducing power, in the form of say ascorbic acid, glutathione or alkalinizing nutrients would be of help to the sickle cell sufferer in this regard. They would do this by free-radical-scavenging, reduction of acidity and the enhancement of ATP hydrolysis efficiency.

Enhancing glucose and pyruvate metabolism and hydrogen ion excretion, perhaps more than anything, would enhance the energy efficiency of the SCA blood system; lowering the resting energy expenditure. Achieving this would improve the energy status and general well-being of the sickle cell sufferer.

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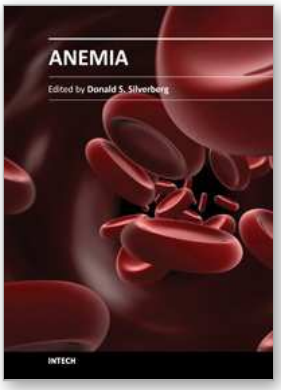

Anemia

Edited by Dr. Donald Silverberg

ISBN 978-953-51-0138-3
Hard cover, 440 pages
Publisher InTech
Published online 29, February, 2012
Published in print edition February, 2012

This book provides an up- to- date summary of many advances in our understanding of anemia, including its causes and pathogenesis, methods of diagnosis, and the morbidity and mortality associated with it. Special attention is paid to the anemia of chronic disease. Nutritional causes of anemia, especially in developing countries, are discussed. Also presented are anemias related to pregnancy, the fetus and the newborn infant. Two common infections that cause anemia in developing countries, malaria and trypanosomiasis are discussed. The genetic diseases sickle cell disease and thalassemia are reviewed as are Paroxysmal Nocturnal Hemoglobinuria, Fanconi anemia and some anemias caused by toxins. Thus this book provides a wide coverage of anemia which should be useful to those involved in many fields of anemia from basic researchers to epidemiologists to clinical practitioners.

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