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Review Article

THE ABO BLOOD TYPE DIET: A REVIEW OF THE HOLOBIONT

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A R T I C L E I N F O

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A B S T R A C T

About a century ago, the ABO blood type was discovered which further divide humanity into four basic blood groups: A, B, AB and O. This new typology is based on well-defined and precise biochemical markers which have been lately demonstrated to influence health and disease. Blood type diets (BTD) have been developed to take advantage of this genetic diversity. The reasons are biochemical in nature. Glycans (special carbohydrates which cannot be hydrolysed by human enzymes), are present in all food items and may trigger immune, inflammatory or tolerance responses. Most recently, a new concept has emerged from life sciences: the holobiont. Humans are metaorganisms and as such are subject to a delicate equilibrium with their proper microbiota. The microbiome is aligned biochemically with the genetics of their host so that everyone has their personalized composition of the microbes. The several variabilities of the ABO blood type can explain this individualization of diet (BTD), which respect the genetic makeup of each person. Notwithstanding this personalization it is still possible to group people into the four blood groups which manifest phenotypically different features. Among these, gastric secretion has been shown to be higher in type O than other blood groups, allowing the former to consume greater amounts of meat (proteins) and easily digest it. In the end, BTD is a form of personalized nutrition that can aid a more holistic approach to health.

INTRODUCTION

It has been known for some time now that relationships exist between humans and resident microbes throughout life which consist of a continuum of mutually beneficial and nonbeneficial conditions (symbiosis, commensalism and parasitism) (1). These relationships closely involve interactions with carbohydrate structures (glycans) expressed by the epithelial cells of the ecological niches where mutual and commensal bacteria reside (2). Experimental findings point towards defined chemical and molecular entities (glycans such as histo-blood group antigens, HBGA) as the basis underlying some if not all of these fundamental relationships (3-5). Both the ABO (codifying for the A, B and O antigens) and the Lewis genes (transcripting for the fucosyltransferase 3 [FUT3] enzyme), with the addition of the Secretor (FUT2) are the main genetic components of the HBGA system (6). The importance of HBGA (especially ABO and Lewis) in the interactions with all microbes cannot be underestimated given their practically ubiquitous presence in the holobiont (7).

We, humans, should acknowledge that our most intimate nature is that of a holobiont, a composite organism constituted by human cells and is microbiome (the highly mutualistic microbial flora) (8).

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A holobiont is therefore an individual with an emergent phenotype composed of both his or her own genome and cells (eukaryotes) and the resident microbiota's genetic material and cells/viruses at any given point in time, forming the hologenome (9, 10). The macrobe (the host) has different forms of interactions (opportunistic, competitive or cooperative) with all of its associated microbiota, including bacteria, archaea, viruses, protists, fungi, and microscopic multicellular animals such as nematodes (11). This new vision of biology, emerging from the ground-breaking researches on the universality and diversity of microorganisms (microbiology), affords a holistic view of biological complexity of human beings (12). Diet, by providing substrates for the bacteria in the colon (the densest and probably the most important of the host-associated microbial communities), contributes to influencing all aspects of human biology and health (13).

Given this new light shining on medicine and health and life sciences, a review of previous findings on blood type diets (BTD) and their newly proposed mechanism of action will aid in our journey towards a more comprehensive medicine (14).

ABO Blood Biotypology

Glycans are known to be involved in the physiologic development of all major diseases (immune diseases, inflammation and cancer), due to their ability to regulate the immune system and be the intermediaries between human cells and the microbiome (15, 16). There is a large body of

evidence pointing directly to ABO, Lewis (Le) and Secretor (Se) glycans as factors implicated in disease susceptibility and microbial interactions (17-20). One possible constitutional approach that can be used in anthropology, and also in constitutional medicine which is always linked to medical information, is blood group categorization (21).

The ABO blood group system was first discovered by Austrian scientist, Karl Landsteiner, in 1900/1901 with three different blood types (A, B and O) and in 1902 the last blood type AB was discovered by two other researchers (22, 23). ABO antigens are oligosaccharides antigens and are widely expressed on the membranes not just of red blood cells (RBC), but also on many other human tissue cells (24). It seems that there are about 2 million ABO antigen sites on RBC, and many are also present on the sensory neurons, epithelium, the vascular endothelium and platelets (25). Biochemically, these four blood types (A, B, AB and O) are inherited through genes on chromosome 9 (at 9q34.1 and 9q34), the ABO locus, which has three allelic forms (A, B and O), and encode for specific glycosyltransferases (26). Since this discovery, many scientists have tried to search for associations between the ABO system of patients and various pathologies (disease susceptibility) (27). Researches were also performed investigating the association of the blood type of individuals with several psychological factors such as personality (28). In 1927, for example, based on blood types, Furukawa Takeji distinguished people into four temperament types: A, B, AB, and O (29).

The ABO blood group system forms a typology. The ABO system can be expressed in a typological field (a fourfold table), where each of the possible combinations are called constructed types (30). This is represented in Table 1.

Table 1 ABO Blood-Type System

Antigens	A	~A (non-A)
B	AB (universal receiver)	B
~B (non-B)	A	O (Universal Donor)

The ABO, Le and Se phenotypic expression (glycans) are intimately linked together as the ABO defines the ultimate structure of the glycan (A, B. or O, from the α-2-fucosyltransferase [FUT1 (H)]) while FUT3 (Le) adds a fucose in α-3 to the base glycan and FUT2 (Se) adds a fucose in α-3 in exocrine secretions (31). Hence, the ABO phenotype imposes limitations to the type of glycans being expressed by Le and Se genes, while Lewis and Secretor type imposes more variability on the manifestation of such glycans in humans. To wit, a person with blood type A will have only A antigens expressed in the Lewis form (including Le^x/Le^y, ALe^b or ALe^y, but not BLe^y), while a blood type O individual will have no A or B antigens (only Le^x/Le^y and Le^b) (32). The ABO blood group antigens are graphically represented in Figure 1.

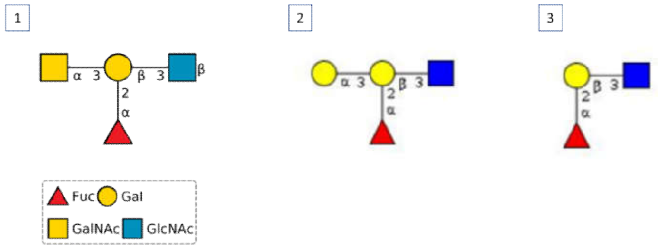

Figure 1 ABO Blood Groups

Legend: Typical cartoon representation of 1. Blood group A, 2. Blood group B, 3. Blood group O.

ABO and Lewis can be expressed on lipids (glycolipids), proteins (glycoproteins) in both O- and N-glycan forms and without a carrier (free forms).

Variabilities

There exist some variants within both the A and the B antigens so that these are classified as subgroups by the quantity of the relative antigen present (33, 34). An initial layer of variability is shown in the presence of A and B subgroupings. Weaker phenotypes of both A and B antigens have been identified and studied at a genetic level and result from polymorphism (base substitution or deletion/frame shift) of the ABO gene (35). Experiments have shown that all rare A and B subgroups display weaker serological reactivity compared to A_1 or B (36). These are shown to be less expressed on the erythrocytes, to give weaker reactions or to be nonreactive serologically with anti-A or anti-B antisera and can easily be mistyped as blood group O individuals (37).

These are defined with progressive numerals indicating a smaller amount of the sites or density of the determinant on the RBC, with relative loss of agglutinability and function: A_1, A_2, A_3, A_x, etc. (38). Although this polymorphism is known (as a result of genetic mutation) and accounts for effective subgrouping (39), the impact on the classification system is negligible.

Those with weaker genetic A or B antigen will phenotypically display ever more characteristics resembling an O blood type and thus will be closer to a combined/mixed constitution (something like an A/O and B/O).

Within the ABO subgroups, the weaker phenotypes of both A and B antigens are shown on the erythrocytes to give weaker reactions or to be nonreactive serologically with anti-A or anti-B antisera and can easily be mistyped as blood group O individuals (37).

To visualize this graphically, Figure 2 describes the various weaker phenotypes on a continuum and their 'relative' closeness to (distance from) the O blood group (in descending order of site density from the point of the arrows).

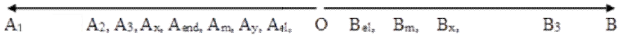

Figure 2 ABO Subgroup Continuum

Note: The B subgroups are identical to the A with the exception that there is no B_2, B_{end}, and B_y. Polymorphism of the O blood glycan is not shown for simplicity.

The importance of this typology lies in the fact that the ABO system can easily identify a biological marker to assess the influence of genetic factors of the individual (40). Moreover, it has recently been proposed that the oligosaccharides (glycans) that form the ABO system are fundamentally correlated to a myriad of different biochemical functions in the human body (14). As the glycome is comprised of many glycans often attached to proteins and lipids as a result of multiple competing enzymatic activities, it has often been neglected as too complex to study (41). But, the technology is now available to start looking into these critical molecules. Cell surface glycans (in the form of a dense coat called the glycocalyx), extracellular matrix-related and secreted protein

glycans seem to be essential for life, co-opting for innumerable intrinsic functions (42). Extensive reviews of literature and advances in the field of glycobiology have confirmed the multifaceted features and physiologic functions of these molecules (43).

Further layers of variability may be added if considering other HBGAs, such as P1PK, Li, GLOB, FORS, etc., though these are limited in their presence (expression) to only some lipids (glycosphingolipids [GSL]) and have a low incidence of variation (apart from P1/P2) (44). A final layer of variability can be seen in the presence or absence of the Rhesus factor. Although the Rhesus (Rh) factor is not a glycan but rather a protein, or, better still, a glycoprotein, its physiologic role is yet largely unknown (45). These glycoproteins are of particular importance since they are not only expressed on erythrocytes, but a few Rh protein homologues were discovered present in human and mouse nonerythroid tissues (46).

ABO Blood System

Modern Biomedicine has placed its core on the concept of the uniformity of the human body (i.e., the human body of each individual can be normalized, for all intents and purposes) to standardized and universal biotechnological interventions [(47), pp. 1-2]. The dominance of the natural science model of explanation in biomedicine is manifested in a rational management of disease through the almost total use of technological interventions for the study and practice of medical care [(48), pp. 7-14]. The ABO blood system originates from the technological sophistication of biomedicine following the discovery of plant lectins and the relative development of lectinology as a field of scientific investigation (49).

Lectins are thus important molecules which have been first proposed as a possible mechanism for the successes of the BTD (50). Many plant lectins are known to be resistant to gut proteolysis and displaying biological activity (binding to small intestine) to varying degrees (51). But this explanation, coupled with the limited presence of biologically active lectins foods and in animals, could not explain all of the vast amount of effects noticed with dietary interventions (52). Another mechanism was warranted and was provided with the rise of a new science, glycobiology, aided by the necessary advances in technology. Dietary glycans have therefore been proposed as key players in the mechanism of BTD due to their ubiquitous nature, unique biochemistry and resiliency in the GI tract (14). Glycans on cell membranes are implicated in the formation of lipid rafts, which are assemblies known to be responsible for initiating many signal transduction pathways, including those for immunity (53). The ABO determinants, in particular, were shown to stabilize sialylated clustered saccharide patches (similar to lipid rafts) on the plasma membranes in a differential manner depending on the glycotope (antigen) (54). ABO antigens can therefore alter the presentation of other cell surface glycans (such as sialic acids) to cognate-binding proteins (endogenous lectins) which play important roles in a variety of physiologic and pathologic interactions (55). The end result is that different ABO antigens will create a differential biochemical, immunological and psycho-physiologic response (depending on the individual's biotype) to various internal and external stimuli (15).

It has been anticipated that the symbiotic relationship between the host, and functionally associated prokaryotes, eukaryotes, and viruses in the context of an environment is the holobiont (56). Both endogenous factors, such as host genetics, and exogenous environmental conditions, including stress, hygiene, diet and infections throughout life have a vital part in outlining the unique composition of an holobiont's microbiome (57). An often-underestimated parameter in the determination of the microbiota composition is host genetics and especially the biochemical environment of the niches created by the host.

Glycans, again, come into play in this new paradigm as their interaction with the microbiota is recognised in extant literature (58). Indeed, the biological marker most representative of host genetics is the ABO blood group, a glycan. There are two main reasons for this. The first is the ubiquitous presence ABO glycan antigens in human tissues. The second because the human microbiota, irrespective of location and niche, interacts with the human cells through a complex system of glycan-lectin binding (bacterial glycans with human lectins and vice versa) (52, 59, 60). It has been shown extensively almost two decades ago that microbes align to ABO and histo-blood group antigens (HBGA, like Lewis and Secretor[1] type) present in the GI environment through specific microbial receptors (2, 61). The structural diversity of these glycans seems to play major role in susceptibility and resistance to infections and infectious diseases (5, 62). Furthermore, microbes have glycans on the surface (like all cells) with ABO-like functions (maybe not structures) so that gut microbiota act as an organ having the same blood group antigens as the host (63). Consequently, these microorganisms can be recognized by the host's immune system, in an ABO-dependent manner. Demonstration of this key event comes, for example, from studies on microbial exposure and formation of anti-ABO antibodies (64).

BTD and Microbiota

Apart from the possible associations discovered over the years between the ABO blood types and physiologic (athletic performance) (65) and psychologic factors (66), ABO biotypology resulted important for identifying than individual's diet. The first proposal of a dietary system based on blood grouping, the BTD involved not only differences in susceptibility of disease but also exercise format and lifestyle (50). From that time, BTD and relevant lifestyles were empirically practiced and studied by some physicians with positive results (67).

BTDs have emerged following the realization that certain foods have special biochemical constituents which elicit differential immune or inflammatory responses in different individuals. Dietary glycans have been recognized as the prime source of these different reactions in ABO blood groups (52). These can mimic ABO epitopes and thereby trigger tolerance or immune responses or be preferentially utilized by resident gut microbes in a healthy or deleterious manner (15). Specifically, oligosaccharides present on glycoproteins and glycolipids are not digested by our enzymatic toolkit and will be the object of hydrolytic attack by the much more vast bacterial CAZymes (68)

[1] Secretor is not a true blood group system, but regulates the expression of ABO and Lewis carbohydrates in tissues and exocrine secretions it must be considered an alloantigen system.

It is here where, the microbial community inside the each human holobiont differs not just in terms of anatomy and physiology as outlined above, but also biochemically. Biological diversity, as the result of genetic variations, other resident microorganisms and diseases (acting as essential environmental factors) may have important implications in susceptibility to diseases (cancer, infections, etc.) and in innate and adaptive immune responses (7). The point in common with ABO and microbes is their affinity towards blood group glycotopes. Through interactions with genetically predefined ABO glycans, the complex ecological community of the microbiota has an intrinsic relationship that can influence normal physiology and contribute to disease susceptibility (14, 57, 69). Essentially, each ABO group has its own distinct microbial communities (host-associated microbiota) that define the holobiont, biochemically and patho-physiologically. Ultimately, HBGA (ABO glycans) are central in personalized medicine and in our understanding of the complex network of genes, oncodevelopmental biological processes, and disease mechanisms (44).

ABO Phenotypical Diversity of the Holobiont

One of the many characteristics of the blood group constitutions is the difference seen in stomach acidity between different ABO blood groups. Already in the 1950s, researchers noted relationships between ABO blood groups and gastric secretory function (acid and pepsin production) (70). Although initially the association was seen at a disease level (and hence on a susceptibility basis), it was soon realized that ABO blood grouping and Secretor status were beyond the simple connection with the type of gastric or peptic ulcer (71, 72). It became soon clear that the acidity and volume of basal acid secretion was linked to the ABO blood group with the type O having the highest values, overall (73). This effect may be due to an increased serum level of pepsinogen (as a marker of gastric secretion) in blood type O with respect to type A individuals (and higher males than in females) (74). Similar results were found with pepsinogen A serum levels (75).

So, it is likely that gastric hypersecretion, a major factor in duodenal ulcer, has a constitutional basis-anatomic, genetic, or physiological (76). This fact has obviously important consequences with respect to the holobiont concept of biology of man and related medical applications. Although body habitus has been correlated to both basal acid output (BAO) and maximum acid output (MAO), these was found to be definitely higher in type O than in other ABO blood groups (77). The same is true when considering type O individuals with non-secretor status having higher acidity (hyperacidity) than secretor subjects (78). Moreover, the increased total pepsin production, as noted earlier, in blood type O may play a minor role in the pathogenesis of peptic ulcers but has to be viewed in light of its enzymatic function coupled with hyperacidity (79).

The acidity and the pepsin/pepsinogens work together in the context of the stomach's role in chemically breaking down food and, specifically, denaturing proteins (80). Pepsin is a proteinase that hydrolyses the amide bonds within proteins in the presence of acid, like gastric juice (81). Pepsinogen, secreted by chief cells (stimulated by gastrin) needs high acidity conditions (hydrochloric acid produced by the parietal cells, stimulated again by gastrin) to be transformed into pepsin, the main gastric protease (82). Therefore, pepsin and a highly acidic environment are fundamental in denaturing proteins (likely from animal sources). A simple comparison of the stomach pH across animals by taxonomic group, clearly identifies humans with an average gastric pH of 1.5 at the level of facultative scavengers and surely within the domain of generalist carnivores (83). Hence, the higher the acidity of the stomach, like in the case of vultures, the better the animal is equipped to consume carrion without suffering any apparent ill-effects from the toxic metabolites excreted by microbes decomposing the carcass (84). Apart from the role of disinfection (a pH < 3 is bactericidal), a highly acidic stomach is conceivably more helpful for denaturating proteins, as gastric acid activates pepsinogen into pepsin to initiate protein digestion (85). Also, pepsin is biologically active at pH < 4, since gastric refluxate becomes caustic at this pH range and translates into erosive esophagitis (86). Finally, the lower stomach pH of type O subjects, coupled with greater quantities of pepsin/pepsinogen, translates into a more carnivore constitution (requiring to digest more proteins).

CONCLUSIONS

Recent advancements in scientific understanding continuously confirm the truth of the definitions of biotypes exclusive to each individual. Especially, the holobiont concept opens up new prospects of understanding human health and nutrition (16).

The interactions between microbiotas and their hosts (wherever they reside in the host's body, blood, brain or gut) characterise the holobiont as a unique and single biological entity (87, 88). This uniqueness is defined by the presence of special glycans that form the ABO blood group antigens, which separates each human being into four distinct groups. Even more exceptional is the variability present inside this typology which explains the diverse reactions that each individual experiences with the same foods.

A few examples of this variability has been presented as already understood and appreciated in medical literature. The main example, the higher gastric secretion output of type O blood group persons, shows how diversified human beings really are and how they can be suitably grouped into categories (biotypes) for the sole purpose of identifying disease susceptibility and possibly host-microbial interactions.

Hence, the need for a more tailored approach of medicine is paramount and is actually materializing as it slowly shifts its focus from a materialistic to a multi-omics viewpoint (personalized medicine) (10). Medicine should embrace the hologenomic perspective that a systems-level framework for host biology is necessary to explain the complex etiologies of diseases, giving rise finally to precision medicine (9).

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