Malglycemia and Cancer: Introduction to a Conceptual Model

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Purpose/Objectives: To introduce a conceptual model detailing the physiologic contributions of malglycemia to cancer formation and increased morbidity and mortality.

Data Sources: A literature search was conducted using the PubMed, CINAHL®, and Cochrane databases, as well as Surveillance, Epidemiology and End Results (SEER) cancer statistics.

Data Synthesis: Multiple complex factors are associated with malignancy formation, proliferation, and outcomes for each individual. The authors present a model, termed the Malglycemia Orbit Model, that is analogous to an atom, centered on a core of individual factors, and surrounded by "orbits" containing cancer and related factors. Highlighted in this model is the role of malglycemia.

Conclusions: Cancer formation and sequelae involve numerous multifaceted factors. One factor not well described or understood within the context of malignancies is glycemic status, most notably how malglycemia impacts cancer formation and risks for adverse outcomes. The atomic-structured malglycemia model describes this process.

Implications for Nursing: Among the many uncontrollable factors that contribute to cancer formation and adverse outcomes, malglycemia is one that is modifiable. Nurses are in a prime position to conduct research to enhance understanding and ultimately improve protocols for better glycemic control and, in effect, better outcomes for individuals with cancer.

The annual incidence of cancer worldwide is estimated to reach 17 million by 2020 and 27 million by 2050 (Parkin, Bray, Ferlay, & Pisani, 2005). The lifetime risk of developing any type of cancer for someone born today is more than 40% (Howlader et al., 2011). A complex interplay exists between factors that contribute to the formation and proliferation of malignancies, as well as to treatment complications and decreased survival. A study by Hammer et al. (2009) has shown that malglycemia (abnormal glycemic status) is a risk factor for infection and mortality among patients who received allogeneic hematopoietic cell transplantation (HCT) for hematologic malignancies. Based on those findings, the theoretical associations between malglycemia, malignancy formation (and related treatments), and sequelae throughout the body will be explored.

Malglycemia is defined as any blood glucose (BG) measurement outside of the normal range of 70–125 mg/dl, including hyperglycemia (BG of 126 mg/dl or greater), hypoglycemia (BG of less than 70 mg/dl), and/or increased glycemic variability (standard deviation between BG measurements of 29 mg/dl or greater) (Hammer et al., 2009). Patients with cancer with or without preexisting diabetes may be at increased risk for experiencing malglycemic events during and following treatments for cancer because of older age (Stookey, Pieper, & Cohen, 2004; Vischer et al., 2009), high body mass index (BMI) (Roumen, Blaak, & Corpeleijn, 2009), nutritional imbalances (Butler, Btaiche, & Alaniz, 2005; Jenkins et al., 2002; Martin-Salces, de Paz, Canales, Mesejo, & Hernandez-Navarro, 2008; Sheean & Braunschweig, 2006), low physical activity levels (Katz, 2007; Moien-Afshari et al., 2008), high stress levels (Butler et al., 2005; Godbout & Glaser, 2006; Turina, Christ-Crain, & Polk, 2006), treatment with glucocorticoids (Butler et al., 2005; Mazali, Lalli, Alves-Filho, & Mazzali, 2008; Willi et al., 2002), and treatment with other chemotherapeutic agents or immunosuppressants (Mazali et al., 2008; Ramos-Cebrian, Torregrosa, Gutierrez-Dalmau, Oppenheimer, & Campistol, 2007), as well as from infections themselves (Turina et al., 2006).

Malglycemia also may contribute to the onset of cancer. In a joint statement by the American Cancer Society and the American Diabetes Association, strong epidemiologic evidence suggests that diabetes is a risk factor for certain malignancies including cancers of the

liver, pancreas, and endometrium and, to a lesser degree, cancers of the colon, rectum, breast, and bladder (Giovannucci et al., 2010). Compared to the prevalence of diabetes in the general population (11%) (National Institute of Diabetes and Digestive and Kidney Diseases [NIDDK], 2011), as many as 18% of patients with cancer also have preexisting diabetes at the time of the cancer diagnosis (Barone et al., 2008).

The conceptual framework for how malglycemia contributes to complications in patients with cancer and the onset of cancer itself has not been well described. The purpose of this article is to introduce a conceptual model detailing the etiologies of malglycemic states in patients with cancer and the physiologic contributions of malglycemia to cancer formation and increased morbidity and mortality.

The Malglycemia Orbit Model

Cancer, related treatments, and associated complications often are multifaceted and mostly nonlinear in nature. To depict and best visually describe the complexity and dynamic quality of the interrelationships between the components, the authors created a visual model structured like an atom (see Figure 1). In the model, the central core contains concentric circles depicting individual underlying factors including genetic, epigenetic, environment, lifestyle, and comorbidities. Three orbits surrounding the central core contain elements (analogous to an atom's electrons) and are paired per orbit as follows: cancer and treatment, impaired immune function and infection, and malglycemia and normal blood glucose. These paired elements, reflective of electrons circulating around the core of an atom (American Nuclear Society, 2011) are in constant motion articulating with the central core and one another, depending on the interplay of all the influencing factors at any given time. The entire model is then surrounded by the potential outcomes of survival or death.

The malglycemia-normal blood glucose orbit is highlighted and poised as the vertical central orbit in the model to visually depict the influence of glucose on all elements, particularly the overarching influence of malglycemia. Because blood glucose levels can be quite variable (Hirsch & Brownlee, 2005), the element of malglycemia is paired with normal blood glucose to capture such fluctuations in patients with cancer.

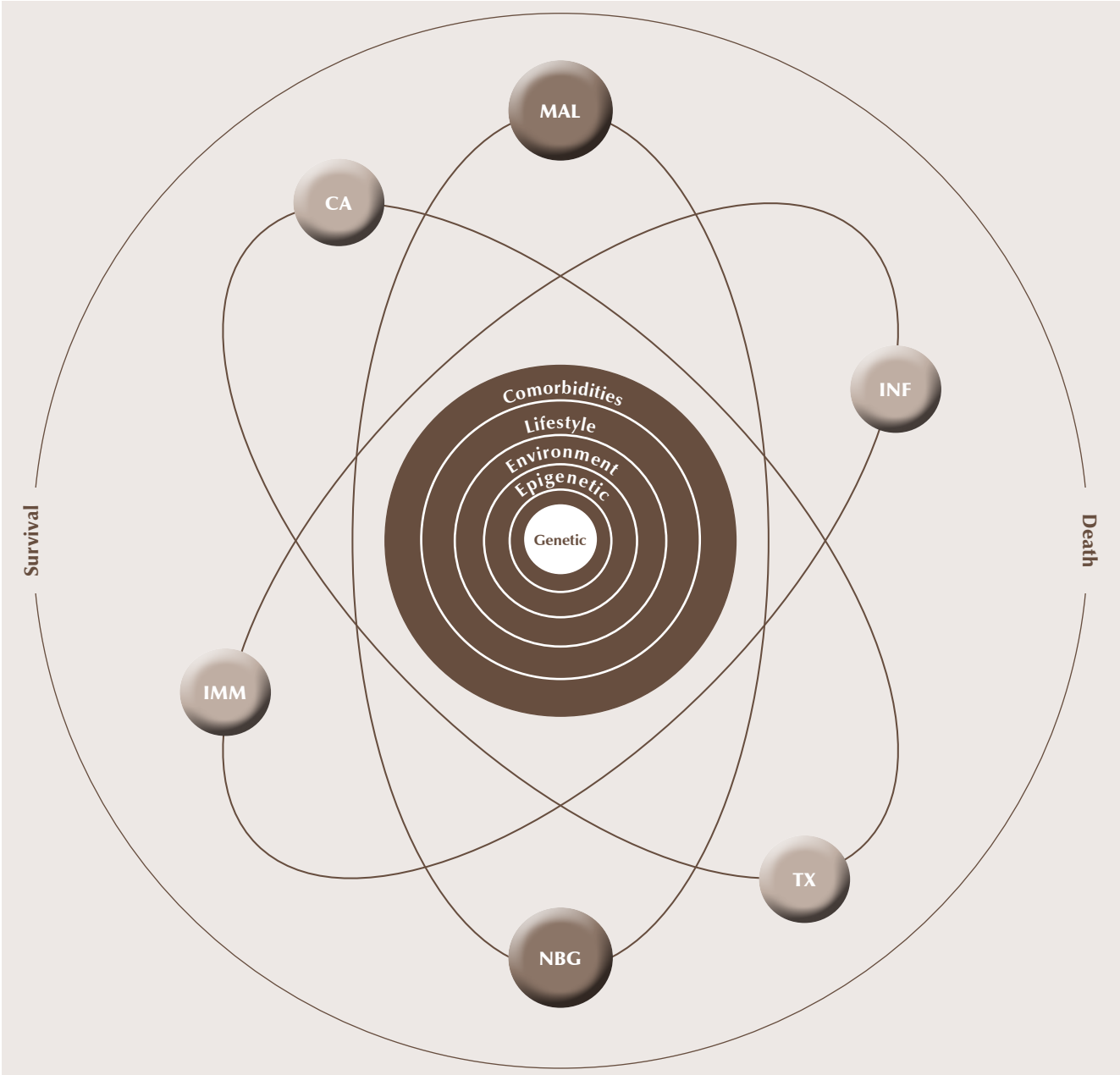
Malglycemia

Malglycemia is multifaceted in its onset and complex in its role in association with cancer. Hyperglycemia and glycemic variability (fluctuations outside of normal glycemic parameters) induce oxidative stress leading to physiologic complications systemically (Hirsch & Brownlee, 2005; Monnier, Colette, & Owens, 2008). Studies using intensive insulin therapy in critically ill patients have been mixed, showing decreased morbidity and mortality by reducing hyperglycemia (van den Berghe et al., 2001) and also increased mortality from induced states of hypoglycemia (Braithwaite, 2008). In patients with cancer, particularly in those receiving HCT, all three components of malglycemia have been found, but predominately remain in the hyperglycemic and, to a lesser degree, increased variability ranges (Fuji et al., 2007; Hammer et al., 2009). Hyperglycemia with concomitant insulin resistance and lack of insulin secretion defines diabetes (Giacco & Brownlee, 2010) and can be associated with increased risk for malignancy onset (Giovannucci et al., 2010) and mortality in patients with cancer (Barone et al., 2008).

With or without a history of diabetes, malglycemia can occur in patients with cancer and its deleterious influence can be systemic. Of particular importance is malglycemia's impact on immune function, as the immune system plays an integral role in the prevention of cancer and infections. The role of malglycemia-induced immune alterations is best understood through the hyperglycemic pathway. The process begins with the elevated blood glucose levels that cannot be reduced to a therapeutic range through normal homeostatic mechanisms.

Mitochondria and Reactive Oxygen Species

Mitochondria are intracellular organelles responsible for producing cellular energy, maintaining cellular ion concentrations or regulating reduction-oxidation (redux) reactions (the transfer of electrons between molecules, ions, or atoms), and moderating cellular apoptosis (Yu, Jhun, & Yoon, 2011). The process of creating cellular energy requires the production of adenosine triphosphate (ATP) (Brownlee, 2005; Green, Brand, & Murphy, 2004; Yu et al., 2011). ATP is created from the actions of the electron transport chain (ETC)—an electrochemical gradient that is established across the inner membrane of the mitochondria. Electrons are transferred across the ETC, creating a proton pump of activity as protons (positively charged particles such as hydrogen ions) are moved across the membrane (Brownlee, 2005; Yu et al., 2011). The energy created from this electrochemical activity drives the phosphorylation of adenosine diphosphate (ADP) via the enzyme ATP synthase to create ATP (Green et al., 2004). Under normal circumstances, about 95%–96% of the oxygen used during mitochondrial metabolism is reduced to water with the remainder creating reactive oxygen species (ROS) (Klaunig & Kamendulis, 2004). ROS is part of the cell's regulatory process in mediating



CA—cancer; IMM—impaired immune function; INF—infection; MAL—malglycemia; NBG—normal blood glucose; TX—treatment

Figure 1. Malglycemia Orbit Model

cell growth, migration, differentiation, senescence, and apoptosis (Ziech et al., 2010). When aberrations occur in the ETC, the normal electron flow is disrupted, resulting in a disproportionate production of ROS (Brownlee, 2005; Yu et al., 2011).

ROS is created in excess when the amount of oxidants produced exceeds the amount of antioxidants (Klaunig & Kamendulis, 2004). Sources of the creation of this imbalance include endogenous cellular events within the organelles, including mitochondria, endoplasmic reticulum, and peroxisomes (Klaunig & Kamendulis, 2004; Velayutham, Hemann, & Zweier, 2011), and through exogenous sources such as white blood cell activity (Klaunig & Kamendulis, 2004). One of the intracellular events creating ROS is the production of inflammatory cytokines (Klaunig & Kamendulis, 2004), which can be triggered by hyperglycemia (Esposito et al., 2002).

Glucose Metabolism and Oxidative Stress

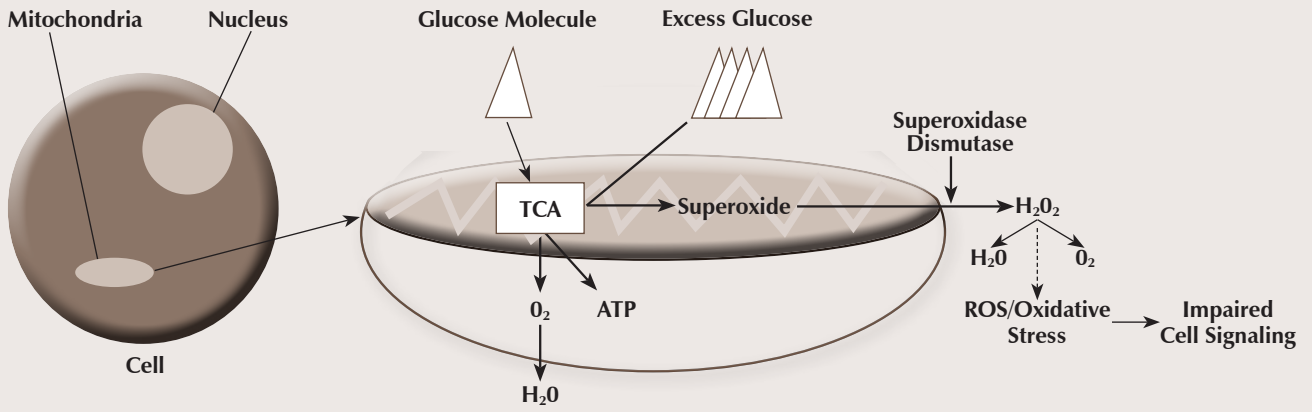
Glucose is needed for cellular function and comes from our diet through the digestion and intestinal absorption of carbohydrates, and through the processes of glycogenolysis (the conversion of glycogen stores in the liver to glucose) and gluconeogenesis (the formation of

glucose from noncarbohydrate molecules in the body) (Giugliano, Ceriello, & Esposito, 2008). The body regulates glucose to maintain a level of circulating glucose in the blood with normal fasting blood glucose levels between 70 and 130 mg/dl and less than 180 mg/dl two hours following the start of a meal and with a glycated hemoglobin less than 7% (American Diabetes Association, 2011). Regulation of glucose is dependent on feedback mechanisms and hormone release, including glucagon and insulin from pancreatic alpha and beta cells, respectively (Kawamori, Welters, & Kulkarni, 2010), and the glucokinase regulatory protein in the liver, pancreatic beta cells, neurons, pituitary, and enteroendocrine cells (Massa, Gagliardino, & Francini, 2011). In addition, autonomic nervous system control via hypothalamic neuroendocrine activity plays an integral role in blood glucose regulation, including the modulation of substances such as leptin, a hormone that regulates appetite (Kalsbeek et al., 2010). This complex and multifaceted system works harmoniously to keep glucose levels regulated within a relatively narrow therapeutic range. When out of balance, the adverse sequelae can be far reaching.

Viewing this balance on an intercellular level, the normal glucose metabolic pathway involves processing glucose molecules through the tricarboxylic acid cycle in the mitochondria (Brownlee, 2005). Essentially, the glucose is transformed into molecular oxygen, which eventually converts to water. This process is part of the pathway in which ATP is synthesized through the ETC. With excess glucose, the system is overwhelmed, creating an overabundance of molecular oxygen or superoxide (Brownlee, 2005). The enzyme superoxidase dismutase breaks down the superoxide to hydrogen peroxide, which subsequently dissociates it into oxygen and water (Brownlee, 2005; Giacco & Brownlee, 2010). The metabolism of the resultant oxygen creates an overabundance of ROS, creating oxidative stress causing interference with normal cell signaling (Brownlee, 2005; Giacco & Brownlee, 2010) (see Figure 2).

Hyperglycemia and Cell Signaling

Hyperglycemia-induced oxidative stress, in effect, alters cell surface and cytosol pattern recognition receptor function within innate immune cells that normally detect pathogen-associated molecular patterns (one of the ways immune cells recognize foreign molecules) (Janeway & Medzhitov, 2002; Mendelsohn, Howley, Israel, Gray, & Thompson, 2008; Pickup, 2004). Hyperglycemic states activate toll-like receptor pattern recognition receptors, causing a cascade of signals within the innate immune cells (Esposito et al., 2002; Giugliano et al., 2008; Mendelsohn et al., 2008). This signaling cascade evokes activation of nuclear-factor kappa B (NF-κB), signal transducer and activator of transcription-3, and hypoxia-inducible factor alpha transcription factors that induce cytokine, chemokine, and prostaglandin expression (Mantovani, Allavena, Sica, & Balkwill, 2008). In particular, the proinflammatory cytokines interleukin (IL)-1β, IL-6, IL-8, IL-18, and tumor necrosis factor-alpha (TNF-α) are expressed (Esposito et al., 2002; Mendelsohn et al., 2008). The sequelae of these events leaves the natural white blood cell activities such as complement fixation, cell adherence, chemotaxis, phagocytosis, and direct killing of infectious microorganisms to become compromised and allow infections to ensue (Butler et al., 2005).



ATP—adenosine triphosphate; H_2O_2—hydrogen peroxide; ROS—reactive oxygen species; TCA—tricarboxylic acid

Note. The mitochondria organelle is the site of cellular energy formation converting a glucose molecule, shown here, to ATP after processing through the TCA cycle. Excess glucose converts to superoxide producing H_2O_2 via superoxidase dismutase. The resultant ROS creates oxidative stress, which impairs cell signaling.

Figure 2. The Physiologic Impact of Hyperglycemia

Note. Based on information from Brownlee, 2005; Giacco & Brownlee, 2010.

In addition to those events, hyperglycemia also can trigger the release of cortisol, epinephrine, norepinephrine, glucagon, and growth hormone, leading to increased insulin resistance, lipolysis, gluconeogenesis, glycogenolysis, and decreased insulin secretion, all further promoting hyperglycemia (Smiley & Umpierrez, 2010). Concurrently, hyperglycemia stimulates increased levels of cytosolic calcium that induce mitochondrial fragmentation causing increased ROS and oxidative stress (Yu et al., 2011). Figure 3 illustrates how hyperglycemia compounds the inflammatory process within the cancer model.

Malignancy

Malignancy formation is a multistage process that includes factors that initiate, promote, and progress the abnormal cell development (Deng, Liu, & Du, 2010; Mendelsohn et al., 2008). One of the processes that circumvent endogenous mechanisms that prevent aberrant cell formation is immunoediting—a sequence of cellular events that shift from accurate immunosurveillance and related malignancy-preventing activities to epigenetic alterations (Germenis & Karanikas, 2007). As malignancies form, neovasularization to the tumor site occurs accompanied with the production and release of cytokines from the tumorigenic tissues. That activity solicits innate immune cells to the local tumor environment. In addition, those innate immune cells activate the secretion of the interferon-gamma (INF-γ) cytokine. INF-γ, along with proinflammatory cytokines, create an inflammatory response that, in turn, solicits cells of the adaptive immune system (Pawelec, Derhovanessian, & Larbi, 2010; Smyth, Dunn, & Schreiber, 2006). At this state, immunosurveillance from these white blood cells involves the proper detection of the aberrant tissue formation and subsequent action to arrest its development. Malglycemic states impair this process through the overexpression of proinflammatory cytokines, causing an inhibition of proper cell signaling, and, therefore, preventing proper responses such as apoptosis. The impaired immune response contributes to the stage of immunoediting called escape—the immune system fails to detect the aberrant cell formation, allowing the malignancy to prevail (Dunn, Old, & Schreiber, 2004; Germenis & Karanikas, 2007; Smyth et al., 2006).

Contributors to Malglycemia and Malignancy

Many factors contribute to both malglycemia and malignancy onset, and each of these can be mutual risk factors. Figure 4 shows the associations. Malglycemia, particularly the component of hyperglycemia, clearly interferes with normal mitochondrial activity (and to a lesser degree, other intracellular organelles), impairing the ability of the immune cells to respond effectively to foreign microorganisms and aberrant cell formation. The causes of malglycemic events in patients with cancer are many and not isolated to patients with preexisting diabetes. The contributors to both malglycemia and malignancy include older age, poor nutrition, high BMI, low physical activity, physiologic and emotional stress, and infections. Medications such as glucocorticoids and certain chemotherapeutic agents inhibit malignancies but contribute to malglycemic events.

Older Age

Risks for both malglycemic states and malignancy increase with advanced age. For example, compared to the prevalence of diabetes in adults aged 20 years and older (11%), the prevalence of diabetes among adults aged 65 years and older is 27% (NIDDK, 2011). Cancer incidence also increases with advanced age (Giovannucci et al., 2010). The mean age of cancer onset is 66 years, and 54% of cancer incidence occurs in individuals aged 65 years and older (Howlader et al., 2011). In addition, compared to the population at large, patients with cancer have a higher prevalence of diabetes at the time of the cancer diagnosis (Barone et al., 2008). The exact underlying physiology is unclear; however, it may involve increased plasma hypertonicity which has been associated with insulin resistance or impaired glucose usage and hyperglycemia (Stookey et al., 2004). Plasma hypertonicity is more prevalent in older adults with dehydration related to diet, exercise, and medications (Stookey et al., 2004). Plasma hypertonicity and other factors of aging, such as cellular senescence (Campisi & d'Adda di Fagagna, 2007) and immunosenescence may predispose older adults to malglycemic states, even without a history of diabetes. Immunosenescence, the age-related decreased functional capacity of immune cells (Fulop et al., 2010), also may predispose patients with cancer (Freund, Orjalo, Desprez, & Campisi, 2010).

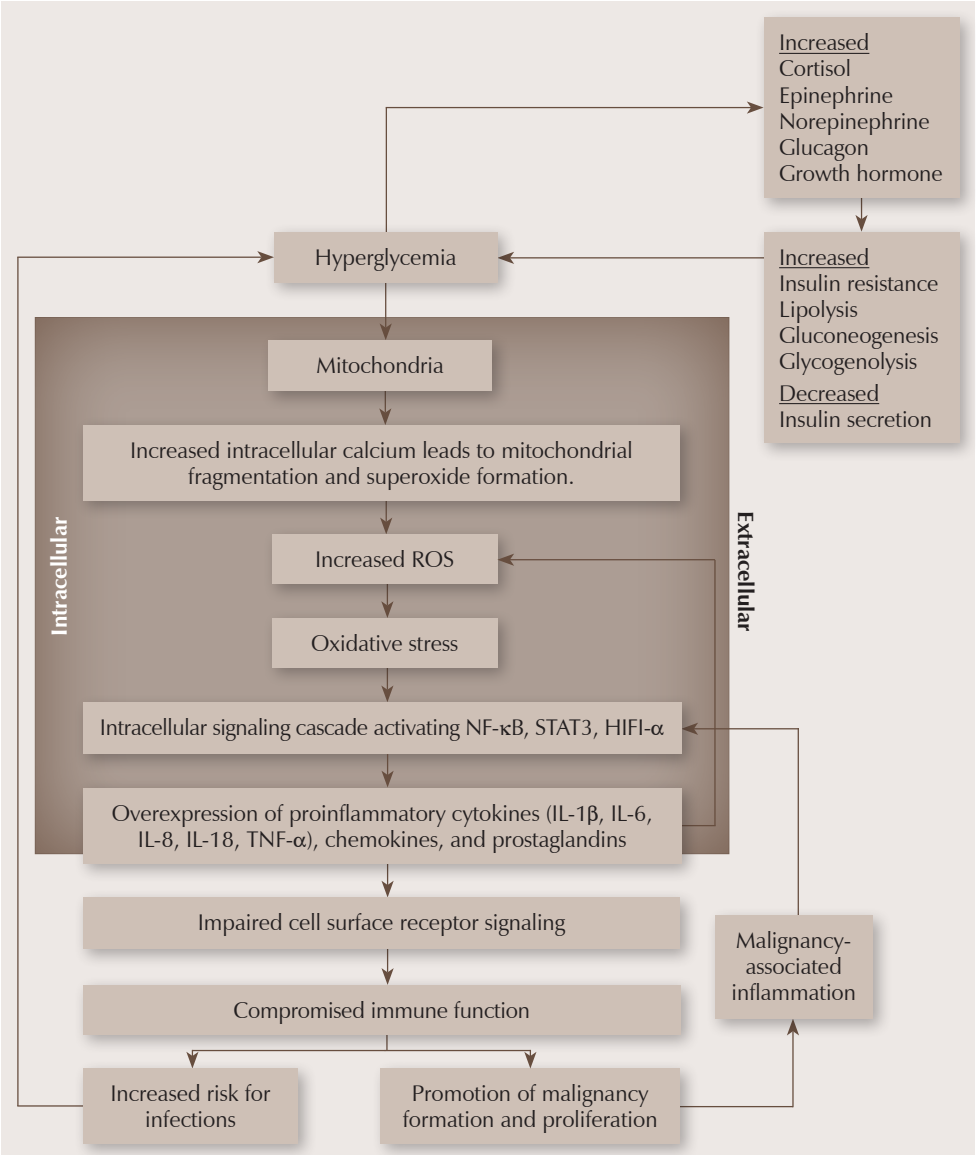
Regarding malignancy onset, cellular senescence is the loss of cellular replicability from endogenous and exogenous stressors that cause aging and damaged tissue, degenerative age-related pathology, and/or premalignant lesions (Campisi, 2011). Cellular senescence of nonimmune cells on a DNA level involves the progressive loss of telomeres—the nonfunctional end nucleotides that act as protective caps for the functional inner DNA strands of chromosomes (Campisi & Yaswen, 2009; Rodier & Campisi, 2011). With each cell replication, the telomeres shorten and, eventually, the functional components become compromised (Kuilman, Michaloglou, Mooi, & Peeper, 2010). The enzyme telomerase protects against telomere attrition and cellular senescence and, through this, preserves cellular function (Grimes & Chandra, 2009); however, it normally

exists in very few cell lines in humans (Campisi & Yaswen, 2009). Cellular senescence is induced by stressors in the cellular microenvironment, most notably oncogenic stress (Campisi, 2011; Campisi & d'Adda di Fagagna, 2007), and acts as a protective mechanism against cancer through impeding cell replication (Coppe et al., 2008). When tumors form, telomerase then becomes abundantly expressed, thus allowing tumor cells to proliferate indefinitely (Campisi & Yaswen, 2009; Grimes & Chandra, 2009; Rodier & Campisi, 2011). Both epidemiologically and physiologically, older age is seen as a risk factor for malglycemia and malignancy onset. Once cancer has manifested, the risk for malglycemic states in older adults is even greater (Hammer, Motzer, Voss, & Berry, 2010).

Poor Nutrition, Low Physical Activity, and High Body Mass Index

Poor nutrition and low physical activity are related to high BMI and all are independently and synergistically associated with malglycemia and malignancy predisposition. Diets consisting of foods with a high glycemic index (the rate or degree to which a carbohydrate-containing food will raise an individual's blood sugar) and glycemic load (the amount of carbohydrates available in a particular serving of food and its glycemic index) are known contributors to obesity (BMI greater than 30) (Esfahani et al., 2009; Giovannucci et al., 2010; Livesey, Taylor, Hulshof, & Howlett, 2008). Low physical activity, particularly compounded with high glycemic foods, accelerates the road to obesity (Zinn, 2010). Obesity is an exponentially growing problem worldwide with a prevalence of more than 300 million individuals (Zinn, 2010). Obesity is highly associated with insulin resistance and type-2 diabetes (Giovannucci et al., 2010) and is a risk factor for malignancy onset (Giovannucci et al., 2010; Hursting & Berger, 2010; Zinn, 2010). Excess body weight, even prior to a BMI in the obese range, is associated with increased risks for various malignancies including gastrointestinal and hepatobiliary cancers (Kant & Hull, 2011). In addition, the risk for mortality increases exponentially and significantly at obese states with a 44% increased risk for death with a BMI level between 35 and 40 and a 251% increased risk when the BMI exceeds 40 (Berrington de Gonzalez et al., 2010).

Evaluating the content of foods themselves, some contain genotoxic substances (agents that cause direct



HIFI-α— hypoxia-inducible factor-alpha; IL—interleukin; NF-κB—nuclear factor kappa-B; ROS—reactive oxygen species; STAT3—signal transducer and activator of transcription-3; TNF—tumor necrosis factor

Figure 3. Hyperglycemia in the Inflammation and Cancer Model

Note. From "Cancer-Related Inflammation," by A. Mantovani, P. Allavena, A. Sica, and F. Balwill, 2008, *Nature, 454,* p. 437. Copyright 2008 by Nature Publishing Group. Adapted with permission.

DNA damage leading to mutations) such as those found in fried, broiled, barbecued, smoked, nitrite-preserved, or cured meats; whereas other foods that are classified as nongenotoxic, such as high-fat foods, also can have the ability to activate inflammation and other systemic responses causing cellular aberrations (Sutandyo, 2010). Diets high in red meat increase the risk for stomach and colorectal cancer, saturated fat is a risk for breast cancer, and high amounts of dairy protein and calcium are actually a risk for prostate cancer (Gonzalez & Riboli, 2010).

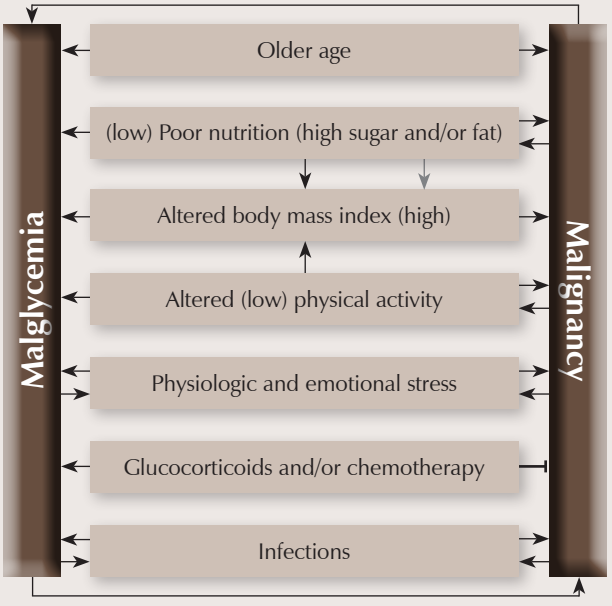
Physiologically, a prolonged inflammatory response is created from obesity. Hyperglycemic states in relation to or independent of obesity that remain high without physical activity to promote cellular uptake of glucose lead to increased levels of oxidative stress which, in turn, promote cellular aberrations and impair mechanisms to counter the aberrations (Anand et al., 2008; Hursting & Berger, 2010; Mathers, Strathdee, & Relton, 2010; Zinn, 2010). In addition, obesity-induced inflammation alters cellular metabolism through modulation of cytokine expression and immune cell function (Kant & Hull, 2011; Nikolajczyk, Jagannathan-Bogdan, Shin, & Gyurko, 2011). Similarly, infectious microorganisms related to obesity, termed infectobesity (Zinn, 2010), also promote inflammatory responses (Anand et al., 2008; Zinn, 2010). Infectobesity is associated with adipogenic pathway activation in humans, including lipid accumulations in preadipocytes, alterations in inflammatory responses, increased insulin sensitivity, decreased leptin secretion, and increased inefficient metabolism (Pasarica & Dhurandhar, 2007), therefore also contributing to states of malglycemia, particularly hyperglycemia, in patients with cancer.

Nutrition becomes further altered once individuals are diagnosed with cancer and undergo treatments. Treatment side effects can alter appetite and taste, leading to malnutrition and associated hypoglycemic states (Pinto & Trunzo, 2005). In addition, patients who experience nausea, vomiting, diarrhea, anorexia, mucositis, and enteritis are at increased risk for nutritional and electrolyte imbalances (Martin-Salces et al., 2008). When total parenteral nutrition is administered to compensate for nutritional deficits, hyperglycemia is a common problem (Pinto & Trunzo, 2005).

Physiologic and Emotional Stress

Stress is another predisposing factor to malglycemia and malignancy onset and progression. Physiologic stress is the body's response to a physical or physiologic event, such as severe illness, that disrupts homeostasis to the extent that it is unable to readily correct the disruption. Severe illness-induced physiologic stress can lead to hyperglycemia from an overexpression of cortisol, glucagon, epinephrine, norepinephrine, and TNF-α, which can result in increased gluconeogenesis, lypolysis, and insulin resistance (Gearhart & Parbhoo, 2006; Leonidou et al., 2007; McCowen, Malhotra, & Bistrian, 2001; Smiley & Umpierrez, 2010). Emotional stress creates a physiologic response similar to physiologic stress, and the two can perpetuate one another.

Characterized as an unfavorable life event with self-perceived ineffective coping ability, emotional stress can be viewed as predominately universal among patients diagnosed with cancer (Costanzo, Sood, & Lutgendorf, 2011). In effect, the malignant tissue triggers immune cell activity, inflammation, and, with solid tumors, angiogenesis, which compositely mediate disease outcomes (Costanzo et al., 2011). The malignant tissue response also induces emotional responses in relation to behavioral or psychosocial factors including, among others, stress, anxiety, and depression that, in turn, activate neuroendocrine and sympathetic responses, which further perpetuate the malignancy response (Costanzo et al., 2011). This physiologic response to emotional stress includes activation of the hypothalamic-pituitary-adrenal axis and autonomic nervous system activation (Armaiz-Pena, Lutgendorf, Cole, & Sood, 2009). In this pathway, hyperglycemia can be viewed as an outcome of stress (Gearhart & Parbhoo, 2006) and a contributor to the malignant tissue response of inflammation and immune activity



Note. Arrows indicate the interrelationships between the contributors to both malglycemia and malignancies and their association with one another.

Figure 4. Contributions to Malglycemia and Malignancy

(Costanzo et al., 2011). A study by Depke et al. (2008) found psychologically induced stress in mice led to hypermetabolic syndrome that included observations of gluconeogenesis, hyperglycemia, and increased lypolysis. In addition, investigators have shown stress to contribute to the initiation and progress of cancer (Armaiz-Pena et al., 2009; Costanzo et al., 2011).

Treatment: Glucocorticoids and Chemotherapy

Once established, the malignancy will interfere with mechanical and physiologic functioning of the body, necessitating interventions as early as possible. Treatments can be as complex as the malignancies and, depending on type, grade, and stage of growth, may include one or more of the following: surgery, chemotherapeutic regimens, radiation, hormone therapy, biotherapy (immunotherapy or biologic response modifiers), and newer targeted therapies all aimed at annihilating or preventing further growth of the malignancy while minimally involving healthy tissue (Hait, Rubin, & Bertino, 2008). The treatments themselves can compound the already compromised immune system created by the malignancy.

Malglycemic states also can be triggered by cancer therapies. In particular, glucocorticoids used as an antiemetic and treatment for its immunosuppressive properties, as well as inducing active malignant cell replication (needed for the chemotherapy to be effective), is a known hyperglycemic-inducing agent (Butler et al., 2005). Other immunosuppressants, such as tacrolimus and cyclosporine, also induce hyperglycemia (Butler et al., 2005; Ramos-Cebrian et al., 2007). Oxaliplatin used as hyperthermic intraperitoneal chemotherapy for peritoneal malignancies (Rueth et al., 2011) and docetaxel and cisplatin used for breast cancer (Lee et al., 2004) have shown hyperglycemia as a side effect of treatment. In addition, hyperglycemia from corticosteroids and L-asparaginase is noted in children being treated with these agents for acute myeloid leukemia (Trelinska et al., 2011). Glucose variability also is noted in this population with fluctuations to hypoglycemic states in some cases with use of purine analogs during maintenance therapy (Trelinska et al., 2011).

Another phenomenon regarding solid tumors is their use of glucose to promote their proliferation, also leading to dysregulation of normal glucose metabolism and contributing to malglycemic states. The phosphatidylinositol 3-kinase (PI3K)/AKT (protein kinase)/mammalian target of rapamycin (mTOR) (PI3K/AKT/mTOR) is a pathway involved in cancer cell signaling (Albert et al., 2010). Rapamycin is an antimicrobial medication and immunosuppressant, and mTOR kinase was named for the fact that rapamycin inhibits its action (Albert et al., 2010; El Mjiyad, Caro-Maldonado, Ramirez-Peinado, & Munoz-Pinedo, 2011). Uninhibited, the PI3K/AKT/mTOR pathway promotes cancer cell growth and proliferation and is activated by glucose, oxygen, amino acids, and mitogens (Albert et al., 2010). The use of rapamycin and targeted mTOR inhibitors, or rapalogues, can block this pathway to an extent, but resistance is encountered in some cancers (Albert et al., 2010). Newer mechanisms are focused on glucose deprivation to inhibit this pathway (El Mjiyad et al., 2011). The pathway emphasizes the deleterious effects of hyperglycemia on cancer progression.

Malglycemia also may play a role in the delivery and metabolism of antineoplastic agents. The glucose-regulated protein 78 is overexpressed in tumor cells and one of the pathways activated by this cell surface receptor is the AKT, which suppresses apoptosis, and upregulates NF-κB (stimulating proinflammatory cytokine expression) and other mechanisms, allowing proliferation of malignant cells (Sato, Yao, Arap, & Pasqualini, 2010). In addition, tamoxifen has been found to inhibit gluconeogenesis and stimulate glycolysis in a rodent study (Marek, Peralta, Itinose, & Bracht, 2011). The influence of varying glycemic states on therapeutic agent activity is less clear and necessitates additional investigation.

Infections

Patients with cancer are susceptible to opportunistic infections because of their induced states of immunosuppression from the malignancy and related treatments. Hyperglycemia enhances this process through triggering prolonged proinflammatory cytokine expression leading to impaired immune cell signaling, including INF-γ, that inhibits the detection and elimination of foreign microorganisms (as well as inhibiting abnormal cell formation) (Germenis & Karanikas, 2007; Mendelsohn et al., 2008; Reiman, Kmieciak, Manjili, & Knutson, 2007). Infections ensue and further contribute to hyperglycemic states (Turina et al., 2006). In patients receiving HCT for hematologic malignancies, bacteremias (Poutsiaka et al., 2007), fungal infections (Barnes & Marr, 2007), and viral infections, particularly cytomegalovirus disease (Ljungman, 2007), are common. A study in patients with solid tumors found bloodstream infections, including gram positive and negative bacteremias, anaerobes, fungi, and polymicrobial organisms, prevalent (Anatoliotaki et al., 2004). Infections and related complications such as sepsis can further complicate malignancy treatment and ultimately lead to death independent of the malignancy (Bertz et al., 2003; Hamalainen et al., 2009; Nichols, 2003). The full scope of infections and related complications is extensive and complex, and merits description beyond the scope of this article.

The Inner Core

The center of the inner core of the atom model is the genetic component reflecting the underlying molecular DNA structure that is packaged within the nucleus of each cell (Baylin, 2008). Epigenetic determinants surround the genetic center and represent the expression of genes that are unique to each individual and influence the health and illness continuum throughout a lifespan (Hochedlinger & Plath, 2009; Wilson, 2008). Aberrations can occur at this genetic level throughout life, including the involvement of improper methylation (Baylin, 2008; Watanabe & Maekawa, 2010). Oxidative stress is one contributor to methylation aberrations (Watanabe & Maekawa, 2010), and hyperglycemia can induce oxidative stress (Giacco & Brownlee, 2010) as described earlier in this article. In malignancies, hyper- and hypomethylation of DNA have been associated with various types of cancer. For example, hypomethylation has been found in specific genes in colon cancer (Kulis & Esteller, 2010); whereas hypermethylation has been associated with the *BRCA1* gene mutation in breast and ovarian cancers (Kulis & Esteller, 2010).

Surrounding the epigenetic ring is the environment component. The environment plays a key role in the development of numerous cancers, including solid tumors and hematologic malignancies (Burke & Wei, 2009; Wogan, Hecht, Felton, Conney, & Loeb, 2004; Ziech et al., 2010). An underlying mechanism for malignancy formation from pollutants and chemical exposures is the drastic increase in cellular ROS from environmental toxins leading to nuclear DNA mutations with subsequent malignancy formation (Klaunig & Kamendulis, 2004). Again, the contribution of malglycemic-induced oxidative stress can compound this process. The environment also can represent an individual's family, home, and community life, which may be influenced by any number of factors, including stress and related coping mechanisms described earlier in this article.

Lifestyle surrounds the environment ring and reflects the influence they have on one another. As previously described, nutrition, physical activity level, and, as a consequence of these factors, BMI influence malglycemic states and malignancy risk (Esfahani et al., 2009; Giovannucci et al., 2010; Zinn, 2010). Other detrimental factors related to lifestyle include alcohol, tobacco use, and poor sleep. Alcohol and, in particular, tobacco are highly linked to various types of cancers because of their numerous carcinogen-promoting properties (Anand et al., 2008; Moeller & Sun, 2010). The subsequent inflammatory process, further enhanced by hyperglycemic states (Giacco & Brownlee, 2010), causes tissue damage, extensive over time, leading to malignancy formation (Koul & Arora, 2010). Sleep deprivation further compromises homeostatic mechanisms, contributing to obesity and related health issues (Zinn, 2010). In addition, ethnicity and culture may influence lifestyle behaviors. These factors may be more related to access to health care and disease stage at diagnosis (both of which may be influenced by insurance coverage, geographic location, socioeconomic factors, psychosocial behaviors, and cultural factors) than underlying biologic variations (Serna et al., 2003).

The final concentric ring in the center of the model is comorbidities, multiple health issues as a reflection of negative influences from the inner ring factors. As previously noted, the incidence and prevalence of cancer is highest among older adults (Howlader et al., 2011) and, with advancing age, the prevalence of comorbidities increases (Pal & Hurria, 2010). Eighty percent of individuals aged 65 years and older have one or more chronic condition (Yancik, Ganz, Varricchio, & Conley, 2001). Concurrent with a cancer diagnosis, older adults can have a variety of conditions including diabetes, chronic obstructive pulmonary disease, cardiovascular disease, and/or arthritis (Yancik et al., 2001). Patients with cancer with comorbidities are at greater risk for complications and often treatments are modified because of the concurrent conditions. Oncologists weigh the risks of the malignancy prognosis against the state of comorbid conditions and make treatment decisions often based on their judgment of life expectancy, as no evidence-based practice guidelines exist for making such decisions (Pal & Hurria, 2010). Some outcomes evidence does exist between cancer types and having certain comborbid conditions. For example, patients with diabetes and colon cancer have an increased risk of cancer recurrence and mortality (Yancik et al., 2001). Some comorbid conditions also share similar contributing factors. Obesity and/or a sedentary lifestyle increases the risks for cancer, cardiovascular disease, cerebrovascular disease, and type-2 diabetes (Schottenfeld & Beebe-Dimmer, 2006).

Summary

Cancer, treatments, and the related sequelae are complex processes with varying outcomes for each individual. Part of the complexity and heterogeneity of outcomes can be attributed to the vast macro- and microenvironmental differences for each patient. One contributory element being recognized, but currently understudied and underemphasized in this process, is glycemic status. Malglycemic states can occur from a variety of sources, compromising immune function and leaving the host susceptible to infections, cancer onset, and adverse outcomes. Of importance, this model details how many of the same etiologies predispose individuals

to both malglycemia and cancer and, in effect, malglycemia and cancer are risk factors for one another.

Implications for Practice

As information continues to emerge about the contributions of malglycemia to malignancies and related outcomes, the need for new and innovative interventions for enhanced glycemic control is becoming more evident. Contributors to malglycemic states are multifaceted and interventions to best control glycemic levels need to match each of these facets. Enhanced protocols for better nutrition, weight control, and stress will be part of the armament added to existing pharmaceutical measures (not discussed in this article) for promoting normoglycemic states. Better glycemic control should ultimately lead to a decrease in malignancy onset and a reduction in infections and related complications, including nonmalignancy-related mortality among individuals who develop cancers. Nurses are in a prime position to conduct research to enhance understanding and ultimately improve protocols for better glycemic control and, in effect, better outcomes for individuals with cancer.

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