Boston College

William F. Connell School of Nursing

FACTORS ASSOCIATED WITH REFEEDING HYPOPHOSPHATEMIA IN ADOLESCENTS AND YOUNG ADULTS HOSPITALIZED WITH ANOREXIA NERVOSA

a dissertation

by

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submitted in partial fulfillment of the requirements

for the degree of

Doctor of Philosophy

May 2019

Factors Associated with Refeeding Hypophosphatemia in Adolescents and Young Adults Hospitalized with Anorexia Nervosa

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Abstract

Refeeding Hypophosphatemia (RH) is the most common complication of nutritional restoration during medical hospitalization for individuals with anorexia nervosa (AN). Characterized by a drop in serum phosphorus levels, consequences of RH can be seen throughout the body and are potentially life threatening. Despite the seriousness of this outcome, little is known about which individuals with AN are at greatest risk of developing RH and best practices for prevention. The purpose of this retrospective cohort study was to examine demographic, feeding, and biochemical factors found in hospitalized adolescent and young adults (AYA) diagnosed with AN that may contribute to the development of RH. Individuals diagnosed with AN who were admitted to Boston Children's Hospital between the years of 2010-2016 were considered for inclusion. Three hundred charts were analyzed using logistic regression to determine factors associated with RH and multivariate regression to determine factors associated with serum phosphorus nadir. In the final logistic regression model, receiving nasogastric tube feeding ($p=0.54$), age at admission ($p=.022$), weight gain during hospitalization ($p=.003$), serum potassium level ($p=.001$), and serum magnesium level ($p=.024$) significantly contributed to the model. Odds of RH were 3 times higher in those who received NG feeding, 1.2 times higher for each year of increasing age, 1.5 times higher for each kilogram of weight gain, 9.2 times higher for each unit reduction in potassium, and 13.7 times higher for each unit reduction in magnesium. With regards to phosphorus nadir, 1-unit increase in magnesium resulted in 1.2

increase in phosphorus, and each unit of admit BMI increased phosphorus by .060. The results indicate that NG feeding, age, weight gain, electrolyte abnormalities, and admit BMI are potential indicators of development of RH in AYA hospitalized with AN. This study will inform clinicians of risk factors associated with RH, and may guide further investigation into the clinical management of AYA diagnosed with AN.

Keywords: anorexia nervosa, feeding and eating disorders, hypophosphatemia, adolescent, young adult, refeeding syndrome

Acknowledgments

This work is first and foremost dedicated to my husband, Brendan Kells. With Brendan in my corner, I can accomplish anything knowing that someone believes in me, loves me, and supports even my wildest dreams. Listening to the trials and tribulations of my doctoral program, celebrating the triumphs, soothing in the defeats, caretaking for our two sons while I wrote, Brendan showed me what it means to truly put another first. He has made me the person, wife, mother, friend, and now PhD-prepared nurse I am today. Fr. Michael Himes once said, "loving, not being loved, is the central fundamental part of being human." In that regard, Brendan is the most human person I will ever have the honor and privilege to know, and I am just that lucky to call him my partner in life.

Second, this work is dedicated to our two boys, Henry Phillip and Benjamin Linden. Becoming a mother to those two has been the greatest joy of my life. Throughout this degree, they in equal parts slowed me down and pushed me forward. I hope I made them proud and that they are encouraged to go after their own dreams knowing I am right behind them, win or lose. Most importantly, I hope if they get the choice, they dance.

I have deep gratitude for my mentor, advisor, and committee chair, Dr. Susan Kelly-Weeder. Dr. Kelly-Weeder told me in my first year that getting a PhD would be transformative. She was right on that, and so many things over the 6 years of this work. As a scholar who is committed to not only to research, but also to the success of the students she encounters, I am forever thankful she was assigned as my advisor. Her ability to troubleshoot and assuage my worries while also motivating and moving me forward was invaluable in this process. I could not have done this without her expert guidance, unending reassurance, and sincere encouragement.

I am truly appreciative for my dissertation committee. Dr. Barbara Wolfe, for showing me what it means to be a truly dedicated nurse researcher. I stand in awe of her ability to continually produce the highest quality research while also managing student, faculty, and teaching requirements. Learning from her how to set a plan, outline a timetable, and complete work is something I will take with me throughout my career. The knowledge and guidance she brought to my work is very much appreciated. Dr. Andrea Garber, who agreed to serve on my dissertation committee despite different time zones and her own ongoing proficient body of work is something that I will always be thankful for. Her wisdom moved my work to places it would not have been without her. Dr. Matthew Gregas, who met with me more times than he signed up for, talked me through all of my redundant and novice questions, and was always up for talking about our kids.

Thanks and love to all of my fellow PhD students, with special appreciation to Karen Jennings, Julie Dunne, Amanda Lulloff, Debra Lundquist, and Mary Antonelli. Your companionship and cheerleading was treasured. I am forever changed and continually better from the 14 years (and counting) of knowing Kiely Murray. Your friendship means the world to me.

I am thankful for my parents, Joe and Mary DeMaina, who always knew I would get this degree even when I didn't know it myself. My brothers, Chris and Dann DeMaina, who would drop everything and come to me if I needed them to. The Kells family- Kim, Gerry, Conor, Lauren, Ryan, and Kathryn- who lift my spirits every time we are together. Just knowing that I have my family behind me has made me stand taller.

Lastly, I must gratefully acknowledge the Boston Children's Hospital Inquiry Drives Excellence into Action (IDEA) Grant for generously supporting this work and the University Fellowship of Boston College for supporting my doctoral program. The Institutional Center for Clinical and Translational Research at Boston Children's Hospital and the exceptional Marlon Green, Blair Dykeman, and Sinead Christensen. The Division of Adolescent/Young Adult Medicine at Boston Children's Hospital, and especially the mentorship of Dr. Sara Forman and the support of Moe Melchiono, Dr. Jean Emans, and Dr. Catherine Gordon. Medicine Patient Services at Boston Children's Hospital, with thanks to Jayne Rogers. The staff of 7 West, and the patients who have taught me so much about resiliency in the face of adversity. Thank you to all.

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CHAPTER 1

Introduction

This chapter details the problem of anorexia nervosa (AN), with focus on the development of refeeding hypophosphatemia in adolescents and young adults (AYA) diagnosed with AN. The purpose of the study, research questions, and assumptions based on existing knowledge are outlined. The significance of this project with regards to the care for individuals with AN is addressed.

Statement of the Problem

Anorexia Nervosa (AN) is a serious psychiatric illness characterized by energy restriction resulting in significantly low body weight, intense fear of weight gain, behavior that inhibits weight gain, body image disturbance, and undue influence of self-worth on body weight and shape (American Psychiatric Association [APA], 2013). Care for individuals with AN occurs across medical and psychiatric clinical settings of varying intensity dependent on the case (APA, 2013). Medical hospitalization is required in cases of sustained fasting (food refusal), vital sign instability, electrolyte imbalance, precipitous weight loss, and signs of organ damage (American Academy of Pediatrics [AAP], 2003; American Dietetic Association [ADA], 2001; APA, 2006; Golden, et al., 2003). During medical hospitalization, reintroduction of nutrition is a key component of care. One of the most critical complications of this nutritional restoration period is refeeding syndrome.

Refeeding syndrome is a potentially fatal condition that occurs due to electrolyte and fluid shifts when nutrition is reintroduced to the starved person (Fuentebella & Kerner, 2009). Refeeding hypophosphatemia (RH), a hallmark of impending refeeding syndrome, is the most common complication associated with nutritional restoration in severely malnourished individuals with AN (Skipper, 2012). Although a lower percent of median body weight (%mBMI) on admission has been associated with higher likelihood of developing RH (O'Connor & Nicholls, 2013), contributing individual factors and clinical interventions remain unknown. Therefore, there exists a lack of consensus among providers on best approaches to provide nutritional restoration while preventing RH (Bross, Shah, & Kopple, 2017; O'Connor & Nicholls, 2013). Currently there is wide variability in approaches to nutritional restoration as well as phosphorous supplementation during the refeeding phase (Schwartz, Mansbach, Marion, Katzman, & Forman, 2008).

The prediction of who is at greatest risk of RH remains poorly understood. Initial serum phosphorous levels are likely to be within normal limits (O'Connor & Nicholls, 2013), making admission laboratory surveillance insufficient for identifying potential cases of RH during the medical hospitalization. Additionally, serum concentrations of phosphorous on admission may not accurately predict total body phosphorous depletion that may lead to RH (Winston, 2012), and although phosphorous nadir occurs in the first week of hospitalization for over 80% of individuals during nutritional restoration, nadir may not occur for up to 20% of the population until up to day 24 (Orenstein et al., 2003). Additionally, incidence of RH in adolescents and young adults (AYA) has been reported to be as high as 38%, with an average incidence of 14% (O'Connor & Nicholls, 2013). Therefore, improved identification of those at greatest risk for the development of RH is imperative for improving clinical care in this population.

Purpose of Study

The purpose of this retrospective cohort study is to identify individual factors and clinical interventions that contribute to the development of RH for adolescents and young adults admitted to a general medical unit with AN. The analysis will examine the hypothesis that there is no association between factors identified in AYA with AN who develop RH and those who do not.

Research Questions

1. What factors are associated with the development of RH for AYA with AN during medical hospitalization?
2. How do the factors of interest influence the level of serum phosphorus in this population during medical hospitalization?

Definition of Terms

Anorexia Nervosa: Diagnosable mental illness defined in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* as "persistent energy intake restriction, intense fear of gaining weight or becoming fat, or persistent behavior that interferes with weight gain; and a disturbance in self-perceived weight or shape." (APA, 2013, p. 339). Further sub-classified into restricting type and binge-eating/purging subtypes, with key defining feature between these groups is presence or absence of recurrent binge-eating and purging behaviors within the last three months.

Adolescence: Period of development during which individuals achieve sexual maturation and undergo significant growth and development both mentally and physically. This time in the lifespan is at risk for development of a number of maladaptive behaviors and disorders, including AN. Although onset of physical and sex organ maturation varies between sexes and individuals, commonly used numerical age cutoffs for adolescents is 10-19 years of age (World Health Organization, 2015).

Young Adulthood: Period of the human lifespan between adolescence and adulthood, characterized by life processes such as increasing independence and job/career establishment. Although age cutoffs for young adulthood varies in the literature, for the purposes of this study will be defined as 20-24 years of age, consistent with published literature on risk behavior in the area (Lewinsohn, Rohde, Seeley, & Baldwin, 2001).

Phosphorous: An essential body mineral necessary for energy production in the form of ATP, a component of human DNA, and an acid-base buffer in human blood. Phosphorous is not produced endogenously, but rather is consumed through nutritional intake and primarily stored intracellularly within the body.

Assumptions Based on Existing Knowledge

1. Adolescents and young adults with AN are at risk for RH.
2. Early identification of RH is critical to the care of adolescents and young adults with AN.
3. Nutritional restoration is a primary goal of inpatient medical hospitalization for individuals with AN.

Conceptual Framework

The development of RH is due to the increased production of energy in the form of adenosine triphosphate (ATP) and 2,3-diphosphoglycerate (DPG) as well as a subsequent insulin surge that results in the increased cellular reuptake of serum phosphorus in malnourished individuals. However, factors within the AYA with AN that impact the development of RH within this context remain unknown. Figure 1 illustrates the development of RH in starvation, Figure 2 represents the model of RH for AYA with AN that will be used to guide this research.

Figure 1. Development of Refeeding Hypophosphatemia in Starvation

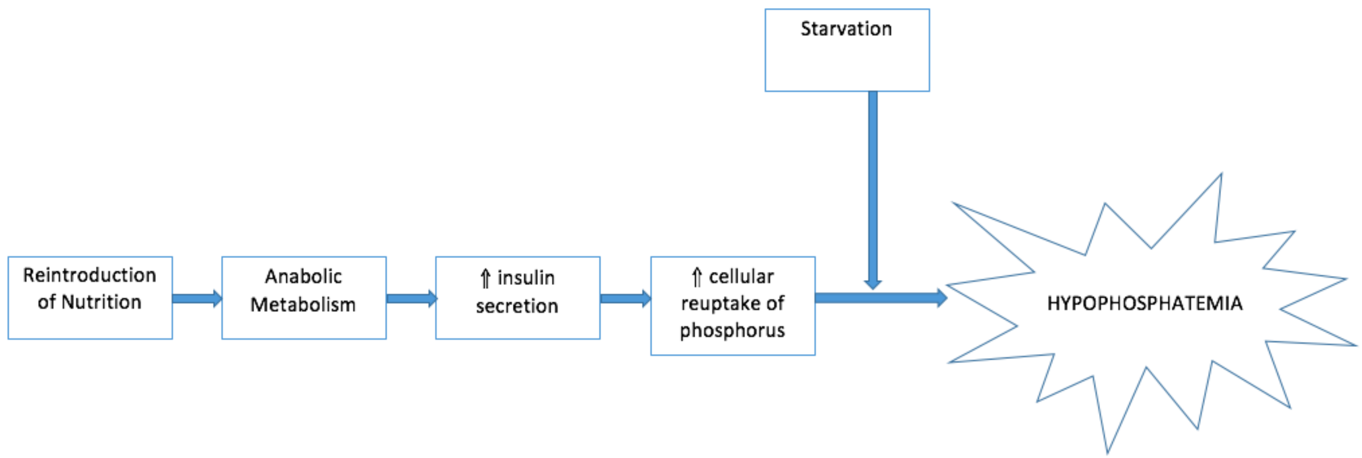
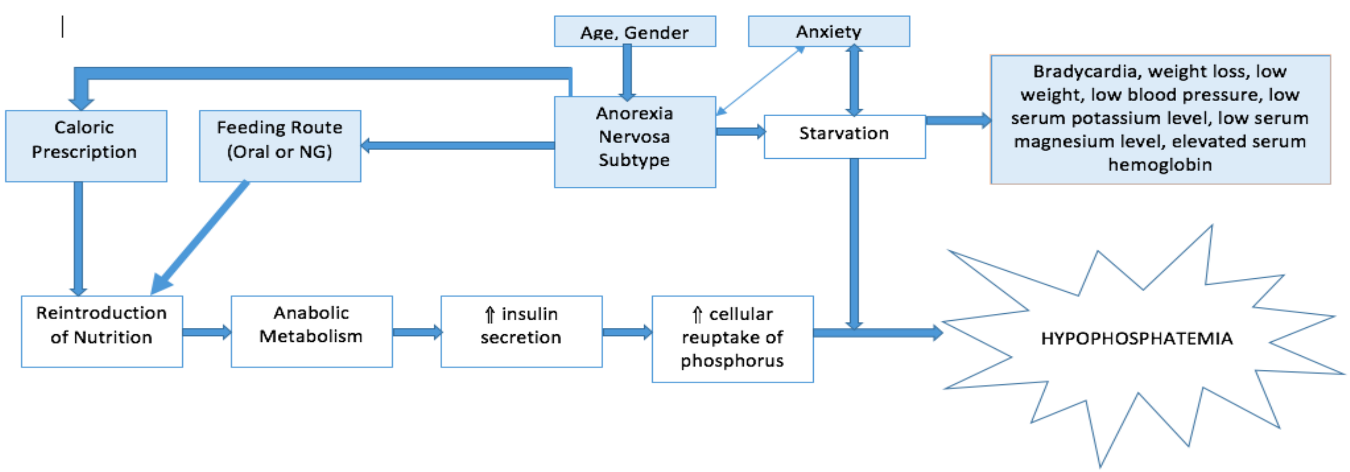


Figure 2. Development of Refeeding Hypophosphatemia in Adolescents/Young Adults with AN with Proposed Predictive Factors



Significance of Project

This study will generate new knowledge on the relationship between factors that are associated with development of RH in AYA with AN. The findings may be used to identify risk and to inform interventions that include individualized care plans for the prevention and management of RH, including appropriate phosphorous supplementation. Furthermore, results may guide clinicians in development of standard protocols and consensus statements on the risk, prevention, and management of RH in this population. Improved prevention and management of RH during medical admission may facilitate timelier transfer to needed psychiatric care for this at risk population.

CHAPTER 2

Review of the Literature

This chapter reviews the literature pertaining to factors that influence the development of RH in AYA with AN during medical hospitalization. This diagnosis of AN will be outlined with regards to epidemiology, medical complications and co-morbidities. A review of refeeding syndrome and RH will be explored. Specific variables of concern include demographic factors including weight/body mass index, weight loss prior to admission, age, and sex will be outlined. In addition, feeding variables including initial caloric prescription and feeding route will be reviewed. Finally, biochemical variables of interest include bradycardia, serum potassium level, serum magnesium level, and elevated resting energy expenditure related to anxiety and psychiatric distress will be examined.

Anorexia Nervosa

First described by Richard Morton in 1859 and termed “anorexia nervosa” in 1873 by Sir William Gull (Pearce, 2004), AN is a chronic psychiatric illness in which individuals inhibit weight gain through restrictive intake, and in some cases use compensatory mechanisms in an effort to avoid weight gain (APA, 2013). AN affects 0.3-2.2% of of the population (Hudson, Hiripi, Pope, & Kessler, 2007; Smink, van Hoeken & Hoek, 2012), with the peak age of onset occurring during adolescence and young adulthood (median 12.3 years; Swanson, Crow, LeGrange, Swendsen, &Merikangas, 2011). There are significant psychiatric and physiologic consequences associated with AN; specifically, AN has been shown to have high mortality rates relative to the population (Birmingham, Su, Hlynsky, Goldner, & Gao, 2005; Papadopoulos, Ekbom, Brandt, & Eselius, 2009), and is suggested to have the highest mortality rate among all mental illnesses (Arcelus, Mitchell, Wales & Nielsen, 2011; Harris & Barraclough, 1998) with one in five individuals with AN suffering death by suicide (Arcelus et al., 2011).

AN is classified into two subtypes: restricting subtype (AN-R), representing those who do not binge eat or purge, and binge eating/purging subtype (AN-B/P), those who report binge eating and purging behavior at least weekly (APA, 2013). In a case report of a low weighted individual, binge eating behavior precipitated hypophosphatemia in itself (Kaysar, Kronenberg, Polliack, & Gaoni, 1991). Purging through the abuse of laxatives or diuretics may influence hypophosphatemia through electrolyte loss during such episodes (Winston, 2012). With regard to illness severity, those with AN-B/P are more likely to relapse (Carter et al., 2012), which may represent more severe illness than those with AN-R.

Medical Complications of AN

AN is associated with a number of medical complications, stemming from malnutrition and compensatory mechanisms to inhibit weight (Monge & Loh, 2018). Physical effects can be seen throughout the body. Some physical effects, such as vital signs or amenorrhea, may resolve with weight restoration, while effects such as low bone mineral density may not (Westmoreland, Kantz, & Mehler, 2016). More commonly seen consequences include cardiovascular compromise (bradycardia, hypotension, arrhythmias), endocrine abnormalities (amenorrhea, euthyroid) and gastrointestinal disturbances (constipation, diarrhea, delayed gastric emptying) and others (Wolfe, Dunne, & Kells, 2016). A summary of medical complications in AN can be found in Table 1. Medical hospitalization for individuals with AN is necessary when an individual exhibits unstable vital signs, or is unable to take food orally, has signs of organ damage, alterations in serum electrolytes, or rapid weight loss (AAP, 2003; ADA, 2001; APA 2003; Golden, et al., 2003).

Table 1.

Medical complications of AN

System	Signs and Symptoms
Cardiovascular	Bradycardia, hypotension, orthostasis, arrhythmias, electrocardiogram abnormalities, sudden death associated with prolonged W-T interval and arrhythmias
Dermatologic	Xerosis, acrocyanosis, brittle hair and nails, hair loss, lanugo, loss of subcutaneous fat
Endocrine	Amenorrhea or ogliomenorrhea, hypoglycemia, alterations in sex hormones, hypothermia, cold intolerance
Fluid and Electrolytes	Dehydration, peripheral edema
Gastrointestinal	Constipation, diarrhea, bloating, gastric distention, delayed gastric emptying, superior mesenteric artery syndrome
Hematology	Bone marrow suppression, anemia, leukopenia, neutropenia, thrombocytopenia, decreased albumin
Musculoskeletal	Fractures, osteoporosis, osteopenia
Neurologic	Depression, syncope, brain atrophy, fatigue
Pulmonary	Pulmonary edema

Note: Adapted from "Nursing care considerations for the hospitalized patient with an eating disorder" by B.E. Wolfe, J.P. Dunne, & M.R. Kells, 2016, *Nursing Clinics of North America,* 51, p. 218.

Co-morbid Psychiatric Diagnoses

High rates of co-morbid psychiatric disorders are reported among individuals with AN (Ulvebrand, Birgegard, Norring, Hogdahl, Von Hausswolff-Juhlin, 2015) with some articles describing up to 97% of individuals experiencing at least one in their lifetime (Blinder, Cumella & Sanathara, 2006). Of those, mood disorders, anxiety, obsessive-compulsive are most common (Hudson, Hiripi, Pope & Kessler, 2007; Swanson, Crow, Legrange, Swendsen & Merikangas, 2011)

Evidence points to an increased prevalence of all types of anxiety disorders including social phobia, obsessive compulsive disorder (OCD), generalized anxiety disorder (GAD), agoraphobia, panic disorder, simple phobia, and post-traumatic stress disorder (PTSD), in individuals diagnosed with AN compared to healthy controls (Godart, Flament, Perdereau, & Jeammet, 2002). Reports indicate that as many as 72% of individuals with AN are diagnosed with at least one anxiety disorder in their lifetime (Godart et al., 2002).

Refeeding Syndrome and Refeeding Hypophosphatemia

Phosphorous

Phosphorus is a mineral that is derived solely from dietary sources (Gropper & Smith, 2013), is found in an abundance of food sources (Anderson & Dempster, 2017; Boyle & Goldfarb, 2017; Heaney, 2012), with high quantities found in dairy products, meat, seafood, and nuts. It is widely found throughout the human body (Boyle & Goldfarb, 2017; Heaney, 2012; Hruska, 2017) and is implicated in bone development, as a component of RNA and DNA, utilized in energy metabolism, is a major component of cellular wall function, and aids in maintaining serum pH (Anderson & Dempster, 2017; Boyle & Goldfarb, 2017; Gropper & Smith, 2013; Heaney, 2012; Raffi & Razzaque, 2017). Digestion of phosphorus occurs through absorption in the intestine (Boyle & Goldfarb, 2017; Gropper & Smith, 2013; Hruska, 2017), and enters the blood approximately one-hour post dietary ingestion (Gropper & Smith, 2013). Phosphorus absorption in the small intestine is mediated by available Vitamin D (Hruska, 2017). The relationship between dietary intake of phosphorus and the absorption of the mineral is linear (Hruska, 2017):as intake of the mineral goes up, so does absorption. Excessive intake of phytic acid, magnesium, aluminum and calcium may inhibit absorption of phosphorus, however this is limited to individuals who receive high doses of antacids or calcium, aluminum, and magnesium compounds (Boyle & Goldfarb, 2017; Gropper & Smith, 2013).

Phosphorus is filtered through the glomeruli of the kidneys, with up to 80-90% reabsorption rate in the renal tubules and increased reabsorption when phosphorus intake is deficient in the diet (Boyle & Goldfarb, 2017; Heaney, 2012; Hruska, 2017). Ultimately, intestinal intake and urine excretion achieve a net balance (Heaney, 2012). Phosphorus is stored in bone, controlled in part through the action of the parathyroid hormone (PTH) and fibroblast growth factor-23 (FGH-23), which regulate bone resorption, movement of both calcium and phosphorus from bone to serum fluids, and renal excretion of excess phosphorus to maintain optimal health (Anderson & Dempster, 2017; Heaney, 2012). Bone loss and formation is constantly in flux in relationship to dietary intake of phosphorus (Anderson & Dempster, 2017). In adult serum, the normal range of phosphorus concentration is 2.5-4.5 mg/ld., with nadir levels of the mineral occurring the morning between 8 and 11 am (Hruska, 2017). Since phosphorus cannot be made endogenously, individuals who do not consume adequate nutrition (i.e., those in starvation state as in individuals diagnosed with AN) will become depleted. Thus, phosphorus deficiency is a considered the hallmark indicator of risk for development of refeeding syndrome (Skipper, 2012).

Refeeding Syndrome

Refeeding syndrome is a constellation of clinical signs and symptoms that occur as a result of metabolic alterations during the reintroduction of nutrition to an individual after starvation state (Fuentebella & Kerner, 2009; Skipper, 2012). What would later be termed "refeeding syndrome" was first described by Ancel Keys and associates at the University of Minnesota in 1944. The Minnesota Experiment utilized conscientious war objectors as subjects to examine the effects of starvation. In this study, thirty-six individuals were randomized to low calorie diets. After achieving significant weight loss, they were refed per protocol with or without vitamin and mineral supplements. During this period of renutrition, Keys documented various signs and symptoms of what is now known as refeeding syndrome, including neurological deficits and peripheral edema (Kalm & Semba, 2005; Keys, Brozek, Henschel, Mickelsen, & Taylor, 1950).

Several years later, Schnitker, Mattman, & Bliss (1951) outline the effects of malnutrition on Japanese prison camp detainees in the Philippine Islands in 1945. In this paper, the Allied medical doctors provided care to 24 of the most severely malnourished individuals out 8,000 prisoners at the camp, consisting of a diet of 3,400 calories, yeast, thiamine, and ferrous sulfate supplementation and compared to 24 healthy Japanese controls. The cases describe edema during refeeding in the majority of cases, dyspnea, palpitations, poor appetite, early satiety, abdominal pain, diarrhea. Weight gain was reported to be "slow" and five of the 24 individuals died. Since that time, the effects of starvation have been studied and described in a number of patient populations, and although proposed guidelines have been suggested (Stanga et al., 2007), a universal definition of the syndrome does not exist.

During starvation, the body attempts to conserve energy by a reduction in basal metabolic rates, insulin secretion, and endogenous hormone production (Fuentebella & Kerner, 2009). To produce energy on a reduced caloric intake, metabolic processes initially deplete fat stores, eventually turning to ketogenesis, and finally to protein catabolism, in turn producing lean body mass and organ atrophy (Bross, Shah, & Kopple, 2017; Fuentebella & Kerner, 2009). During this starvation process, cellular supply of potassium, phosphate, and magnesium are depleted along with fat and protein loss (Bross, Shah, & Kopple; 2017). When nutrition is reintroduced, the shift to carbohydrate anabolism occurs, and a demand for insulin to drive this process develops (Bross, Shah, & Kopple, 2017; Kraft, Ptaiche, & Sacks, 2005). The surge in insulin production results in rapid cellular reuptake of glucose, potassium, magnesium, and phosphorous. The urgent need for phosphorus causes a shift from bone storage of the mineral to cells; however, if starvation induced low phosphorus levels exist prior to reintroduction of nutrition, the high demand for phosphorus is greater than that which bone stores may be able to supply (Boyle & Goldfarb, 2017). Rapid cellular reuptake of phosphorus, along with the state of depleted total body storage of phosphorus during starvation, results in serum levels of the mineral dropping precipitously (Boyle & Goldfarb, 2017; Bross, Shah, & Kopple, 2017; Society for Adolescent Health and Medicine [SAHM], 2014).

The clinical manifestations of refeeding syndrome are largely the result of underlying metabolic and electrolyte disturbances (Bross, Shah, & Kopple, 2017; Kraft et al., 2005). Therefore, consequences of this shift in metabolism can have effects in multiple organ systems and throughout the body. These manifestations may include impaired cardiac function, respiratory failure, neurologic deficits, weakness, paralysis, seizures, arrhythmias, coma, tetany, encephalopathy, nausea, vomiting, constipation, pulmonary edema, lactic acidosis, fluid overload, and death (Kraft et al., 2005).

Refeeding syndrome is not unique to AN; however, this population is at great risk for developing this complication due to nutritional deficiency associated with the disease (Kraft et al., 2005). Refeeding syndrome has been described in those at risk for chronic malnutrition, such as individuals diagnosed with inflammatory bowel disease (Akobeng & Thomas, 2010), post bariatric surgery (Silk, Jones, & Health, 2011; Vincent, Aylwin, & leRoux, 2009) postoperative patients (Geerse, Bindels, Kuiper, Roose, Spronk, & Schultz, 2010), and those in intensive care settings receiving intravenous fluids for extended periods of time without protein or calories (Geerse et al., 2010).

Refeeding Hypophosphatemia

Hypophosphatemia, or below normal levels of serum phosphorous, is the hallmark sign of refeeding syndrome (Kraft, Ptaiche, & Sacks, 2005; Skipper, 2012). The development of hypophosphatemia is multi-factorial. First, during a starvation state the individual becomes depleted of total body phosphorous levels. With the reintroduction of nutrition, the little available extracellular phosphorous is driven intracellularly by a surge in insulin production for anabolism (Boyle & Goldfarb, 2017; Kraft et al., 2005). Finally, the reintroduction of nutrition results in an increased demand for phosphorous as a part of glycolysis, or the production of adenosine triphosphate (ATP) and 2,3-diphosphoglycerate (DPG) necessary for bodily functions (Boyle & Goldfarb, 2017; Haglin, 2001; Kraft et al., 2005; Marinella, 2005).

ATP is the primary energy source for all cells in the body (Kraft et al., 2005), and ATP and DPG are vital to a number of critical body processes (Boyle & Goldfarb, 2017). Therefore, as a result of phosphorous depletion and impaired ATP and DPG production, a number of body systems can be affected. Hypophosphatemia can contribute to the development of seizures (Silvas & Paragas, 1972), inhibited cardiac contractility and function (O'Connor, Wheeler, & Bethune, 1977), respiratory insufficiency (Aubier et al., 1985; Demirjian et al., 2011; Newman, Neff, & Ziporin, 1977), rhabdomyolysis, hemolysis, altered mental status, coma, and death (Kraft et al., 2005). RH is the most common complication associated with nutritional restoration in severely malnourished individuals with AN (Skipper, 2012) and most commonly occurs within the first week of nutritional restoration (SAHM, 2014).

There are no consensus guidelines to provide clinicians with an evidence-based approach to treatment of refeeding syndrome or RH (Boyle & Goldfarb, 2017; Bross, Shah, & Kopple, 2017; O'Connor & Nicholls, 2013; Schwartz et al., 2008), or what what interval is most appropriate for electrolyte monitoring (Boyle & Goldfarb, 2017). The literature reports several common approaches of treatment, including electrolyte replacement when low or deficient (Boyle & Goldfarb, 2017; Bross, Shah, & Kopple, 2017; Schwartz et al., 2008), prophylaxis, and treatment of declining trends. It has been suggested that clear risk stratification to target individuals for whom intervention is warranted is the key fist step in treatment (Boyle & Godlfarb, 2017). Correction of RH is typically either oral or intravenous, based on severity of deficit (Boyle & Goldfarb, 2017).

Demographic Variables

Weight and Body Mass Index

Weight is an important clinical consideration in the classification of the severity and the outcomes of treatment in adolescents with AN (SAHM, 2015). In adolescents with AN, weight classification is best described in terms of the median body mass index (BMI), which is the weight in kilograms divided by the square of the height in inches (Centers for Disease Control and Prevention, 2016). In this age range, median BMI (mBMI) is used as a means of incorporating the adolescent's age and height as weight in absolute number changes according to these demographics (SAHM, 2015).

Weight is used as a treatment outcome and proxy measure in many aspects of care for individuals with AN. It is used as a characteristic in the definition of recovery (Keski-Rahkonen, Raevuori, Bulik, Hoek, Rissanen, & Kapiro, 2014), has been shown to be predictive of favorable short-term clinical outcomes (Lund, Hernandez, Yates, Mitchell, McKee, & Johnson, 2009), the remission of symptoms of AN at the end of treatment (LeGrange, Accurso, Lock, Agras, & Bryson, 2014), and low weight on presentation has been associated with higher mortality rates (Arcelus et al., 2011). Pre-morbid weight has been shown to predict weight at hospitalization discharge, and in turn, weight at discharge predicts weight at 1-year follow up (Focker et al., 2015). Achievement of target weight is also predictive of resumption of menses in adolescents (Dempfle et al., 2013), which is a goal of treatment in this cohort (SAHM, 2015). With regards to psychological outcomes, weight gain improves eating disorder pathology, particularly if achieved earlier in treatment (Accurso, Ciao, Fitzsimmons-Craft, Lock & LeGrange, 2014).

BMI, and mBMI as a more accurate indicator of weight in adolescents with AN, have been associated with hypophosphatemia in this cohort (Ornstein, Golden, Jacobson, & Shenker, 2003). O'Connor and Nicholls (2013) report a positive correlation between percent mBMI and phosphate nadir in a systematic review of RH in subjects with AN, with lower initial % mBMI associated with lower phosphate nadir (r^2=0.6, p=0.01). Golden, Keane-Miller, Sainani, and Kapphahn (2013) also showed an association between percent median body weight (%mBMI) on admission and hypophosphatemia rates during hospitalization (p=0.004) in a cohort of adolescents with AN. Whitelaw et al. (2010) reported a small sample chart audit of 46 admissions that included 29 unique individuals aged 12-18. In this population, those with less than 68% Ideal Body Weight (IBW) were associated with a higher risk of RH, 38% of the admissions showed mild RH and no incidences of "moderate or severe" RH.

Weight Loss Prior to Admission

Weight loss prior to admission is a clinical indicator of severity of illness (SAHM, 2015) and has been suggested as a link to the development of RH (Golden, Keane-Miller, Sainani, & Kapphahn, 2013; SAHM, 2014). In a prospective study of adults with AN, weight loss of greater than 15% prior to admission had sensitivity value of 66.7% in predicting refeeding syndrome, defined, in part, by hypophosphatemia as well as other clinical factors such as hypokalemia, hypomagnesemia, peripheral edema, and end organ failure (Rio, Whelan, Goff, Reidlinger, &

Smeeton, 2012). In a study of hospitalized adolescents with AN, Golden et al. (2013) found an association between hypophosphatemia and rate of weight loss prior to admission (ß=0.2; p=0.03).

Age

The peak age of onset for AN occurs during adolescence (Birmingham, Su, Hlynsky, Goldner, & Gao, 2005; Papadopoulos, Ekbom, Brandt, & Eselius, 2009). The highest incidence is among 15-19 year olds (Wentz, Gillberg, Anckarsater, Gillberg, & Rastam, 2012; Favaro, et al., 2009) and studies suggest that the age of onset has been decreasing over time (Favaro, Caregaro, Tenconi, Bosello, & Santonastaso, 2009). Halmi (2009) has suggested that earlier diagnosis of AN is on the rise. Age at diagnosis is also significant, as earlier initial assessments (those less than 18 years of age compared to greater than 18 and adults) are associated with more favorable outcomes including improved mortality rates (Ackard, Richter, Egan, & Cronemeyer, 2014; Arcelus et al., 2011). Older adolescents have a lower BMI and longer duration of illness on admission compared to younger adolescents (Buhren et al., 2013), Conversely, in a small sample of individuals with AN Wentz, Gillberg, Anckarsater, Gillberg, and Rastam (2012) found that younger age was associated with poorer psychiatric functioning as measured by Global Assessment of Functioning (GAF).

Sex

While AN is predominantly diagnosed in females (Hoek & van Hoeken, 2003), the disorder does affect males. However, there are differences noted in presentation, severity, and pathology in men. Males report significantly more self-induced vomiting than females (Darcy, Doyle, Lock, Peebles, Doyle, & LeGrange, 2012) and may be more likely to diet because they were actually overweight at some point in their lives, as opposed to females who diet because they perceive themselves to be overweight (Wooldridge & Lytle, 2012). Also unlike females, males may have an increased focus on muscle mass, a condition known as "muscle dysmorphia"; however, both genders exhibit similarities in distorted body image, disordered eating, and excessive exercise behavior (Murray, Rieger, Hildebrandt, Karlov, Russell, Boon, Dawson, & Touyz, 2012). Some studies have shown that males self-report excessive exercise at significantly higher rates than females (Lewinsohn, Seely, Moerk, & Striegel-Moore, 2002). Like their female counterparts, males with AN develop endocrinologic consequences/dysfunction, including infertility, low levels of testosterone, Follicle Stimulating Hormone (FSH), Luteinizing Hormone (LH), and Luteinizing Hormone Releasing Hormone (LHRH), and are at risk for the development of osteoporosis (Wooldridge & Lytle, 2012).

Feeding Variables

Nutritional rehabilitation is a primary goal of inpatient medical hospitalization for AYA with AN (SAHM, 2015). Current protocol recommendations by the APA, ADA, and other authorities include a range of caloric prescriptions (ADA, 2006; APA, 2006) which have been suggested to be insufficient for adequate weight gain (Garber et al., 2013; Golden, Keane-Miller, Sainani, & Kapphahn, 2013; Katzman, 2012; LeGrange, 2013; Redgrave et al., 2015; Whitelaw, Gilbertson, Lam, & Sawyer, 2010). Mealtime procedures are of particular interest to clinicians as the need for psychiatric support for this vulnerable population is often greatest during meals (Kells et al., 2016; Long, Wallis, Leung, Arcelus, & Meyer, 2012). The development of RH occurs within the setting of nutritional rehabilitation; therefore, the examination of feeding protocols is a significant component of the discussion of this serious condition.

Initial Caloric Prescription

In a literature review of reports of refeeding syndrome in children and adolescents with AN published by O'Connor and Nicholls (2013), the mean starting rate of caloric intake in cases that developed refeeding syndrome was 27 kcal/kg; however, a wide range of suggested refeeding guidelines which included rates from 10 to 60 kcal/kg were reported (O'Connor & Nicholls, 2013). This review highlighted that even with very conservative approaches utilized to initiate refeeding, individual patients were still at high risk for the development of refeeding syndrome.

A widely accepted, long-standing approach to prevention of refeeding syndrome or RH was the concept of "start low, go slow", with an initial low caloric rate and incremental increase over a period of time such as 4-10 days (Boyle & Goldfarb, 2017). In a systematic review of RH, the studies with the highest initial feeding rates had the highest incidence (O'Connor & Nicholls, 2013). Interestingly, studies that reported low initial refeeding rates also reported the development of RH (O'Connor & Nicholls, 2013); yet, in the final analysis, no correlation was noted between refeeding rate and the development of RH (r=0.21, p=0.7). One study (Leclerc, Turrini, Sherwood, & Katzman, 2013) describes a structured nutritional programs starting at 1500 kcal/day with a relatively low incidence (3.5%) of RH with steady weight gain (Leclerc, Turrini, Sherwood, & Katzman, 2013). However, a number of researchers have argued that initial inpatient feeding regimens are too conservative to support adequate weight gain, and more aggressive feeding regimens have been recommended (Garber et al., 2016; Garber, Michihata, Hetnal, Shafer, & Moscicki, 2012; Whitelaw, Gilbertson, Lam, & Sawyer, 2010; SAHM, 2015).

Feeding Route

Due to the underlying psychiatric nature of AN, extreme fear of weight gain, and gastrointestinal symptomology that may occur during initial nutritional restoration, oral consumption of calories is not always possible. In these cases, as well as other situations where the need to promote weight gain exists, short-term nasogastric (NG) tube feedings to deliver meal replacement formula such as Ensure© or Ensure Plus© may be utilized (AAP, 2003; ADA, 2001; APA, 2006; Golden et al., 2003) and has been suggested to be useful to provide higher amounts of calories than individuals may be able to consume orally (Garber et al., 2016).

In a systematic review of NG feeding in individuals with AN reported by Rizzo, Douglas and Lawrence (2018), studies included showed a less than 1% incidence of RH in those fed via NG tube, with no cases of refeeding syndrome. An integrative review of NG feedings in individuals diagnosed with AN described six studies of examples of resultant RH in NG fed patients (Kells & Kelly-Weeder, 2016). For those examining a cohort of NG fed participants only, Georges et al. (2004) reported one case of severe hypophosphatemia after a 1.2 kg weight gain. Bufano et al. (1990) also described three participants who developed hypophosphatemia two weeks into treatment. Gentile, Pastorelli, Ciceri, Manna, and Collimedaglia (2010) reported hypophosphatemia in 35% of participants on admission, all of which resolved at 30 and 60 days.

When comparing NG versus orally (PO) fed participants, few studies have reported serum chemistry values related to refeeding syndrome. Agostino, Erdstein, and DiMeglio (2013) and Rigaud et al. (2007; 2011) reported no refeeding syndrome for either NG or PO groups; however, in a separate study Agostino and colleagues (2013) reported four cases of RH in the PO group, while no cases were found in the NG fed group.

Biochemical Variables

Heart Rate

Weight loss in AN results in reduced vagal tone which contributes to bradycardia, a common symptom in severely malnourished individuals with AN (Westmoreland et al., 2016)). The degree of bradycardia is a clinical indicator of severity of malnourishment (Galetta et al., 2003). Recent studies have indicated that rate of weight loss is a more accurate predictor of bradycardia than mBMI on admission, suggesting that bradycardia may be a useful clinical tool to indicate degree of malnutrition in individuals with higher weights (DiVasta et al., 2010; Garber, Lee, Benedict, Buckelew, & Moscicki, 2015). In addition to malnutrition-induced bradycardia, severe hypophosphatemia can also impair cardiac function, resulting in reduced stroke volume, mean arterial pressure, and left ventricular stroke work reductions, as well as increases in pulmonary artery wedge pressures (O'Connor et al., 1977). Currently, there are no studies that have examined the relationship between degree of bradycardia and development of RH in AYA with AN.

Blood Pressure

Hypotension and postural changes in blood pressure (orthostatic hypotension) are commonly found medical complications in AYA with AN (Palla & Litt, 1988; Rosen, 2010; Takimoto, Yoshiuchi, Ishizawa, Yamamoto, & Akabayashi, 2014) and are accepted parameters of medical instability necessitating medical hospitalization in this population (SAHM, 2015). When compared with healthy controls, adolescent females with AN demonstrate lower baseline blood pressure (Mirsa et al., 2004) that, unlike bradycardia, may not resolve with nutritional restoration (Shamim, Golden, Arden, Filiberto, & Shenker, 2003).

Potassium

Similar to phosphorous, starvation results in total body potassium depletion. After the reintroduction of nutrition, an insulin surge results in a cellular reuptake of potassium that leads to serum hypokalemia (Fuentebella & Kerner, 2009; Kraft et al., 2005). Hypokalemia has been used as a diagnostic factor in defining refeeding syndrome (Rio et al., 2012) and studies in adult patients have shown hypokalemia as a predictor of RH (Brown, Sabel, Guadiani, & Mehler, 2015).

Magnesium

As with phosphorous and potassium, starvation results in total body depletion of magnesium, as well as a subsequent increase in cellular reuptake of magnesium during the reintroduction of nutrition (Fuentebella & Kerner, 2009; Kraft et al., 2005). Magnesium is a key component of the sodium-potassium ATPase pump; therefore, hypomagnesemia can inhibit potassium repletion (Kraft et al., 2005) and is associated with hypokalemia (Winston, 2012). Intake of magnesium is often low prior to treatment; and therefore, hypomagnesemia may develop prior to or during the refeeding process (Winston, 2012). In a recent study of inpatient adults, low baseline magnesium levels independently predicted the development of refeeding syndrome ($p=.021$; Rio et al., 2012)

Hemoglobin

The hematologic consequences of AN include bone marrow suppression and resultant anemia (Mirsa et al., 2004). However, Brown and colleagues (2015) investigated a sample of adult patients with AN and reported that higher levels of hemoglobin were associated with greater odds of RH (OR=1.56). A possible contributing factor may be hemoconcentration related to dehydration or the use of phosphorous in the formation of hemoglobin itself (Brown et al., 2015). There are no studies to date that have evaluated the relationship between hemoglobin and RH in AYA with AN.

Energy Expenditure and Psychiatric Functioning

As outlined above, weight gain and nutritional rehabilitation are of critical importance in the treatment of individuals with AN. To that end, the topic of resting energy expenditure (REE) has been investigated in an attempt to elucidate factors that may influence weight gain patterns and specific caloric prescriptions for this cohort. REE is defined as the body's energy requirement to fulfill basic physiologic functions while at rest (Castellini et al., 2014). Generally, REE is reduced in individuals with AN compared to healthy controls. This is related to the adaptive state of energy conservation that develops in response to the chronic malnutrition associated with AN (Kosmiski, Schmiege, Mascolo, Guadiani, & Mehler, 2014). However, psychological factors also appear to influence REE in individuals with AN. Anxiety levels were found to be positively correlated with resting energy expenditure (higher levels of anxiety associated with higher REE), while depressive states were reported to be negatively correlated with resting energy expenditure, or that higher depressive state was associated with lower REE (Van Wymelbeke, Brondel, Brun, & Rigaud, 2004). Castellini and associates (2014) reported that psychological distress and lower BMI have been associated with higher rates of REE.

Cellular reuptake of serum electrolytes necessary for energy production is mediated by a person's resting energy expenditure (REE), which is the rate at which a person expends energy at baseline to maintain basic physiologic functioning (Castellini et al., 2014). The higher the rate of REE, the more energy produced and an associated increased need for cellular reuptake of electrolytes. Therefore, it is hypothesized that a diagnosis of anxiety, or impaired psychiatric functioning, may also influence the development of RH in individuals with AN.

Phosphorus Dose

Due to the severity of complications associated with RH, many clinicians recommend phosphorus supplementation during medical hospitalization for AN (Birmingham, Alothman, & Goldner, 1996; Orenstein et al., 2003; Whitelaw et al., 2010). Currently there is wide variability in approaches to phosphorous supplementation during the refeeding phase with some clinicians recommending supplementation only when a patient's serum phosphorous level falls below the reference range value for hypophosphatemia of $\leq$ 2.9 mg/dL, while others supplement throughout the refeeding phase and titrate dosage when the serum level approaches accepted 3.0 mg/dL cutoff (Schwartz, Mansbach, Marion, Katzman, & Forman, 2008; SAHM, 2014).

Summary

The review of literature summarized in this chapter highlights a gap in the knowledge of contributing factors that influence the development of RH in AYA with AN. Although it is understood that %mBMI at admission negatively influences serum phosphorus level during nutritional rehabilitation, body weight alone does not encompass the entirety of the risk in this population. To best understand the development of this potentially fatal complication of nutritional restoration for individuals with AN, analysis which examines multiple co-existing factors that may contribute to the development of RH is necessary.

CHAPTER 3

Methodology

This research study was a retrospective cohort design conducted at Boston Children's Hospital (BCH). Diagnosis of AN was made by the psychiatry team during admission or follow up visits, physician notes, or description of symptoms of AN by report in the psychiatry service note using Diagnostic and Statistical Manual of Mental Disorders, 5th edition ([DSM-V]; APA, 2013) criteria. Cases were individual charts that reported a serum phosphorous at or below 2.9 mg/dL during hospitalization. Controls were those individual charts that reported a serum phosphorous level that never dropped below 3.0 mg/dL during hospitalization.

Setting

Participants were individuals admitted to BCH; specifically, unit 7 West adolescent medicine service. This site was chosen for a number of reasons. First, the investigator has access to this patient population through employment status. Second, BCH is one of the largest pediatric hospitals in the United States and hosts the oldest adolescent medicine service in the country. The division of adolescent and young adult medicine sees over 17,000 patients annually (BCH, 2016), and provides care to adolescents and young adults to age 24 years diagnosed with an eating disorder. The division of Adolescent/Young Adult Medicine hosts grant funded Maternal-Child Health Bureau multi-disciplinary training in adolescent medicine, provides instruction in adolescent medicine for Harvard Medical School, and is a leader in adolescent medicine related scholarship, research, and service. Prior to data collection, consultation with quality improvement specialists at BCH revealed that 95-97 individuals diagnosed with AN were admitted to the target site and unit annually between 2010 and 2014, making this sampling frame likely to have an adequate number of individual records available for analysis. Previous work revealed a rate of 17% hypophosphatemia defined as serum phosphorus ≤ 2.9 mg/dL within the population at the target site (Kells et al., unpublished data). This is consistent with a recent systematic review of RH in adolescents that described a range of 0-38% hypophosphatemia in adolescents with AN (O'Connor & Nicholls, 2013).

Study Sample

The sampling frame included all AYA aged 10-24 years admitted to BCH for treatment of AN, consistent with the age range reported in the literature when examining this topic (O'Connors & Nicholls, 2013) over a seven-year time period from 2010-2016. This time frame started at the most recent complete year that records were available (2016, as study began in 2017) and went back in years until adequate sample size was met. Individuals with multiple hospitalizations were included in the analysis one time using the most recent admission.

Inclusion criteria for medical records to be accepted into the study included age 10-24 years, male and female, admitted to target unit during sampling time frame, diagnosis of anorexia nervosa either binge/purge or restricting subtypes or atypical anorexia nervosa. Exclusion criteria included age less than 10 or greater than 24 years, co-morbid diagnosis of bulimia nervosa, binge eating disorder, serious mental illness including schizophrenia, schizoaffective disorder, medical or psychiatric hospitalization within the last 14 days, feeding method other than oral or NG (gastric tube, TPN). Psychiatric comorbid diseases were included as exclusion criteria due to potential influence these diseases may have on nutritional restoration and psychiatric scores that are included as variables of interest.

Research Design

Research questions were examined using a retrospective cohort design using existing patient medical record data. Initial list of individuals diagnosed with AN were generated using the Childrens360 electronic medical record system. This system provides systematic review of patient charts to generate data. The Childrens360 system was coded to generate a list of all charts in which a clinician billed for AN at any point, utilized the institutional Clinical Practice Guideline (CPG) for restrictive eating disorders, or institutional eating disorder orderset, then narrowed search using inclusion and exclusion criteria. The investigator and two research assistants (RA) hired from the BCH Institutional Centers for Clinical and Translational Research (ICCTR) then reviewed the list generated by Childrens360 for inclusion and exclusion criteria prior to data collection. Charts that did not meet criteria were removed, including four individuals diagnosed with unspecified feeding/eating disorder, seven Avoidant/Restrictive Food Intake Disorder (ARFID), 19 with eating disorder not otherwise specified, and three individuals who received NJ feeds. The initial list generated 350 charts via Childrens360 system during the sampling time frame, charts were entered into the study in backwards chronological order starting with most recent until sample size of three hundred was met.

The Childrens360 system mined data from patient charts including age, admit and discharge dates, sex, ethnicity, race, weight on admission and daily, height, BMI, daily vital signs, and daily laboratory values. The investigator and RAs reviewed Childrens360 data for completion and accuracy, and collected all remaining required data from the existing individual patient medical records using a medical record abstraction tool developed for the study (Appendix A). Data collected by the investigator or RAs included premorbid weight, percent median body weight, Global Assessment of Functioning or Children's Global Assessment Scale score, diagnosis and subtype of anxiety, daily phosphorus dose, and daily formula amount.

RAs received baseline training in research methods and human subjects protection via standard protocol of ICCTR. Additional study specific training for RAs was conducted by the investigator, including study orientation, patient population description, and standard charting specific to diagnosis. For both RAs, investigator performed quality assurance of complete chart review for agreement of the first 5 charts abstracted by RA, the 15^{th} chart (10 charts later), and every 25^{th} chart until completion of study.

Inpatient Protocol

All individuals admitted to the BCH Adolescent Medicine service for evaluation and management of AN were placed on the restrictive eating disorders CPG. This CPG included specific instructions for care including criteria for admission, vital sign and laboratory monitoring, activity, non-adherence guidelines, and nutritional rehabilitation. With regard to meals, after meeting with a dietitian to discuss prior intake and habits, parents were required to make meal selections for all individuals under the age of 18 years. Patients were weighed daily before 7 a.m. after voiding, backward on the scale wearing only a hospital gown and expected to gain at least 0.2 kg per day. Ensure© or Ensure Plus© were given for failure to meet weight gain goals.

Patients were seated in their room for meals, on their bed if vital signs were unstable or in a chair if vital signs were within normal limits and remained on bed rest for at least one-hour post meal. One trained clinician (registered nurse, clinical assistant, or dietician) was present for meal times, in which individuals had 30 minutes to complete all components of the meal. Failure to complete all components of the meal in the allotted time resulted in 20 minutes allowance to complete oral Ensure© or Ensure Plus© replacement under nursing supervision. If an individual was still unable to complete liquid supplementation orally, a NG tube was placed at the bedside and remaining supplementation was given enterally. The NG tube was removed and the patient was offered an oral meal tray at the next meal.

With regards to supplementation, standard practice was that all patients were started on 250 mg twice per day of oral phosphorous supplement as well as a multivitamin on admission. Phosphorus supplementation dose was increased at clinician discretion for down-trending serum level on daily laboratory evaluation or if the level fell below the accepted cutoff of 2.9 mg/dL. There were no written protocols in place with regards to phosphorous supplementation.

Instruments

A medical record abstraction tool was developed by the investigator using Research Electronic Data Capture (REDCap) software (Appendix A). The tool included an assigned unique identifier and all variables listed in Table 2.

The Global Assessment of Functioning (GAF) or Children's Global Assessment Score (CGAS) are brief numeric rating scales that measures an individual's overall level of psychological disturbance. The GAF or CGAS were collected as a measure of psychiatric distress for individuals. The GAF was first introduced by the DSM- III (1980) and from that time has been the most widely used psychological disability assessment in the United States (Gold, 2014). Although the recently released DSM-5 has recommended phasing out the GAF in favor of more specific assessments of functioning, the GAF is still used by many (Gold, 2014). BCH utilized the GAF for all individuals prior to August 2012, and continues to use the GAF as a measure of psychiatric function for some individuals aged 18 and older or at clinician discretion. The GAF has been used for over three decades in myriad of patient populations, in several countries, and across the lifespan including children, adults and elderly individuals (Monrad Aas, 2010). Additionally, the GAF has been used in research studies investigating inpatient populations (Urbanoski, Henderson, & Castel, 2014) as well as adolescent inpatients (Haggerty et al., 2015).

The GAF is comprised of overall assessments of psychological, social, and occupational function (Moos, McCoy, & Moos, 2000). The 0 to 100-point scale is broken into 10-point sections, which have specific associated scoring instructions. Higher scores reflect higher levels of psychological functioning; lower scores signify increasing levels of mental illness. Briefly, a score of 1-10 indicates persistent danger to self/severe mental illness; 11-20 indicates a danger to self/others, failure to maintain hygiene, and impaired communication; 21-30 indicates that behavior is influenced by delusions or hallucinations, impaired communication or judgment, and an inability to function in almost all areas; 31-40 indicates impaired reality testing, communication, as well as major impairments in several areas such as judgment, thinking, and mood; 41-50 indicates serious symptoms or any impairment in social, occupational, or school functioning; 51-60 indicates moderate symptoms or moderate difficulty in social occupational, or school functioning; 61-70 indicates some mild symptoms or some difficulty in functioning but generally has meaningful interpersonal relationships; 71-80 indicates transient symptoms/reactions to stressors; 81-90 indicates absent or minimal symptoms, and general satisfaction with life; 91-100 indicates superior functioning (APA, 2000, p. 34). A score of 0 indicates inadequate information (APA, 2000).

The GAF was adapted by Shaffer et al. in 1983 for use in youth (Shaffer et al., 1983). The adapted tool is titled the Children's Global Assessment Scale (CGAS). The CGAS is used in children, adolescents, and young adults to assess psychiatric functioning as the GAF does in adult populations, using the 10-point system with examples in each section described above. Studies demonstrated adequate discriminant validity comparing inpatient to outpatient settings as well as concurrent validity comparing the CGAS to other measures of psychiatric functioning, specifically the Conners Index (Shaffer et al., 1983) and the Child Behavior Checklist (Bird, Canino, Rubiostipec, & Ribera, 1987; Green, Shirk, Hanze, & Wanstrath, 1994) and among expert consensus (Hanssen-Bauer et al., 2007).

In a study comparing "untrained" and "expert" users of the CGAS, the intra-class correlation coefficient was reported as 0.73 in "untrained" users, and 0.92 in "expert" users (Lundh, Kowalski, Sundberg, Gumpert, & Landen, 2010). In a recent study at BCH, clinicians completed a mandatory training program on the use of the CGAS. Following this program tool accuracy was reported as 80.2%, inter-rater reliability was 0.84 pre-training and 0.95 post-training (Kahn et al., 2014). Beginning in August of 2012, all individuals assessed by the psychiatry consult liaison team in this study were scored using the CGAS. Prior to that date, individuals were assessed using the GAF.

Study Variables

Theoretical and operational definitions of the dependent and independent variables are listed in Table 2. Independent variables were included in the study based on relevant literature review outlined in Chapter 2. The dependent/outcome variable was serum phosphorous level as measured in mg/dL. This variable was measured daily between 9 a.m. and 12 p.m. as per the existing unit protocol. The blood sample was drawn at the bedside by a trained phlebotomist or nurse with phlebotomy training and the results are tested and reported by the BCH laboratory. Serum phosphorous results were obtained from the "lab" section of the electronic medical record.

The independent variables were located in individual patient medical records. Weight, height, and body mass index (BMI) were obtained from the "measurements" section of the medical record. Age and sex were obtained from the "patient profile" section of the medical record. Percent median body weight and caloric prescription were obtained from the dietician notes. Feeding route (oral or nasogastric) were obtained from the nursing documentation flowsheet. Heart rate and blood pressure were obtained from the "vital signs" section of the medical record. Anorexia nervosa subtype, GAF or CGAS score, and diagnosis of anxiety disorder were obtained from psychiatry clinical notes. Serum hemoglobin, potassium, magnesium levels were obtained from the "labs" section of the medical record.

Table 2.

Variables of Interest

Construct	Theoretical Definition	Operational Definition
	Outcome (Dependent) Variable	
Phosphorous Level	Serum phosphorous level measured in mg/dL	Each recorded serum phosphorous level during hospitalization measured in mg/dL in the individual patient medical record, laboratory view
	Predictor (Independent) Variables	
Weight	Body weight measured in kilograms	Body weight measured in kilograms documented in individual medical record the morning following admission within 1 hour of 0600 as per protocol as well as each morning within 1 hour of 0600
Pre-morbid Weight	Body weight in kilograms	Self-reported weight prior to weight loss as documented at any point in the medical record
Age	Age in years of life	Age measured in years recorded in the individual patient record as date of birth
Sex	Sex in male or female	Documented sex of patient; biologic sex if gender transition occurring or occurred as documented in

		the individual patient record
Body Mass Index (BMI)	Weight in kilograms by height in meters squared	Weight in kilograms by height in meters square as calculated by automated formula embedded in electronic medical record software incorporating documented weight and height as recorded in patient medical record within the first 24 hours of admission
Percent Median Body Weight (%mBMI)	Percentage patient body weight of the median (50%tile) BMI for age and height on admission	Percentage patient body weight of median (50%tile) BMI calculated using CDC standardized growth charts, patient age, and patient height on admission as recorded in the patient medical record within the first 24 hours of admission
Heart Rate	Heart rate in beats per minute	Documented heart rate in beats per minute during hospitalization as recorded in patient medical record
Blood Pressure	Blood pressure measured in mm/Hg	Documented blood pressure in mm/Hg during hospitalization as recorded in the patient medical record
Anorexia Nervosa Subtype	Defined by American Psychological Association as Restricting or Binge/Purge Subtypes	Diagnosed APA categorized subtype as assessed and documented by trained mental health clinician in patient medical record at any point during admission
Anxiety Disorder	Defined by National Institutes of Mental Health as: Generalized Anxiety Disorder, Obsessive Compulsive Disorder, Panic Disorder, Post-Traumatic Stress Disorder, or Social Anxiety Disorder	Diagnosed NIMH categorized anxiety disorder as assessed and documented by trained mental health clinician in patient medical record at any point during admission
Global Assessment of Functioning (GAF) or Child's Global Assessment Score (CGAS)	GAF or CGAS on admission	GAF or CGAS as a measure of psychiatric disturbance in range 0-100 as assessed and documented by trained

		mental health clinician within 48 hours of admission
Hemoglobin Level	Serum hemoglobin level measured in mg/dL	Recorded serum hemoglobin level measured in mg/dL recorded in the patient medical record at any point during admission
Potassium Level	Serum potassium measured in mEq/L	Recorded serum potassium level measured in mEq/L recorded in the patient medical record at any point during admission
Magnesium Level	Serum magnesium measured in mmol/L	Recorded serum magnesium level measured in mmol/L recorded in the patient medical record at any point during admission
Feeding Method	Nutritional rehabilitation via either oral or nasogastric route	Feeding route as either oral, nasogastric, or both as documented in the nursing care flowsheet in the patient medical record at any point during admission
Caloric Prescription	Intended calories consumed per day	Calories prescribed per day in kcal as documented by trained dietician in patient medical record
Phosphorus Supplementation Dose	Oral dose of supplemental phosphorus	Daily dose of oral phosphorus given as documented in the medication administration record (MAR) section of the patient medical record

Data Analysis Plan

Statistical analyses were completed using SPSS version 25 © software. Summary descriptive statistics were used to describe the sample and all variables. For both research questions, relationships between independent variables and the dependent variable were examined using logistic regression, chi-square analyses, and one-way ANOVA. Relationships were considered significant if they reached a p value of less than or equal to 0.05.

Testing of assumptions and regression diagnostics were performed. The data was examined for outliers and normal distribution of the dependent variable. Scatterplots were used to examine relationships for linearity between each variable. Correlations between variables were examined using Pearson correlations and tolerance, highly inter-correlated variables were reconsidered prior to entry into model. Distribution was evaluated using histograms of standardized residuals looking for normality of distribution and normal probability plots. Homoscedasticity was evaluated by plotting error variance and examination of residual plot. Standardized predicted values were plotted by standardized residuals to examine for errors correlated with independent variables.

Using the definition of hypophosphatemia as a serum phosphorus level of $\leq$ 2.9 mg/dL (Haglin, 2001; O'Connor & Nicholls, 2013), multiple logistic regression was used to identify factors associated with the outcome (Question 1). All variables were entered simultaneously using the enter method. Multivariate regression was used used to examine the relationship between the independent variables and the dependent variable of nadir serum phosphorus level (Question 2). The multivariate regression was conducted using backward selection. In this method, all variables which meet criteria detailed in bivariate analyses were entered simultaneously and removed by a p value criterion of $\geq$ .10.

Initial Statistical Data Management

All data was collected per above procedures and initially entered into REDCap database. Database was then uploaded into IBM SPSS version 25© for statistical management. Data was examined, missing variables were subject to repeat chart review for thoroughness, and variables were recoded where applicable as described below. Phosphorus dose recorded in mmoL was converted to mg using calculation of 250 mg=8 mmoL. Premorbid weight was calculated by adding reported weight loss prior to admission to admission weight. Where weight loss was reported as a range (for example, 20-25 pounds), the average of the range was used. A number of charts reported actual premorbid weight from previous medical records (primary care records, previous admissions for other diagnoses).

Daily data logs were synthesized into single variables to include in model building. Minimum phosphorus level was calculated from daily phosphorus levels to represent phosphorus nadir, and then recoded into new variable of 0=no hypophosphatemia (nadir never reached ≤ 2.9 mg/dL) or 1=hypophosphatemia (nadir reached level of ≤2.9 mg/dL). Weight gain during admission was calculated by subtracting admission weight from discharge weight. To determine if a participant ever received NG feeding, daily feeding method was recoded as 1=oral feeding, 2=neither/no feeding method recorded, 3=NG feeding, 4=both oral and NG feeding. A new variable was then created in which anything greater than or equal to 3 was recoded to 1=yes (received NG feeding), 0=no (never received NG feeding). Potassium, magnesium, and hemoglobin nadirs were coded using minimum recorded daily laboratory values. Daytime bradycardia was coded as 1=yes, 0=no if any recoded heart rate value was less than 50 beats per minute between 6 a.m. and 10 p.m. Nighttime bradycardia was coded as 1=yes, 0=no if any recorded heart rate value was less than 50 beats per minute between 10 p.m. and 6 a.m. Hypotension was defined as any recording less than 90/50 mmHg. Orthostasis was defined as any recording in which the difference in BP was greater than or equal to 20 mmHg from supine to standing or greater than or equal to 40 beats per minute from supine to standing in accordance with institutional protocol. Total formula in Ensure© and Ensure Plus© in milliliters was calculated by adding all daily values, total calories of formula was calculated by multiplying total milliliters by calories per mL per manufacturer label. Total phosphorus dose was calculated by adding all daily recorded phosphorus supplement doses.

Protection of Human Subjects

Institutional Review Board (IRB) approval was sought through BCH and Boston College (BC). Initial IRB approval was granted at BCH and then reciprocal agreement was obtained at BC. All records were de-identified to maintain confidentiality, each chart was assigned a unique identifier number as it was entered into the study. There were no hard copies of data abstraction tool, electronic records were maintained via REDCAP. Excel file linking medical record numbers to unique identifier numbers were accessible to the investigator solely. The computer used for data analysis was password protected. SPSS files were kept on BC server and not stored on investigators personal computer. Data will be maintained for a maximum of 5 years after completion of the study.

CHAPTER 4

Results

The details of the data analysis and results are presented in this chapter. Specifically, the description of the sample and results of two research questions are addressed. The two research questions were: (1) Which factors best differentiate AYA with AN who develop RH from those who do not? and (2) Do the demographic, feeding, and biochemical variables of interest influence serum phosphorus level in AYA with AN?

Sample Description and Demographics

Three hundred inpatient charts spanning the dates of 9/2010-12/2016 were included in the analysis. The mean age at time of admission was 15.5 years (*SD*=2.5, range 10.1-22.7 years), with a majority of patients representing the adolescent range of 10-19 years (n=288, 96%), and a small sample of young adults aged 20 and older (n=12, 4%). The cohort was primarily female (n=265, 88.3%), and white/Caucasian (88.3%). See Table 3 for additional summary of patient characteristics.

The mean length of stay was 7.36 days (*SD*=5.9). Greater than half (53.3%) of the population were admitted for less than or equal to 6.9 days. A large portion of the sample was diagnosed with AN-R (85%), with smaller groups representing AN-B/P (11.7%), Atypical AN (2.0%), and 1.3% were not subtyped in clinical documentation by psychiatry team. The mean baseline weight on admission was 42.8 kg (*SD*=9.6). Two hundred and ninety-six charts had admission baseline weight and height available for BMI calculation. The mean admit BMI on admission was 16.3 (*SD*=2.6) and average percent median body weight on admission (%mBMI) was 82% (*SD*=12.1).

Table 3.

Demographic Characteristics of Sample

	M (SD)	Range
Age	15.5 (2.5)	10.1-22.7
	n	%
Age Categories		
Child (<10 yrs)	0 (0)	0
Adolescent (10-19 yrs)	288 (96%)	96
Young Adult (20-22.7 yrs)	12 (4%)	
Gender		
Female	265	88.3
Male	35	11.7
Race		
Asian	13	4.3
Black/African American	4	1.3
Other	16	5.3
White/Caucasian	241	80.3
Missing	26	8.7
Ethnicity		
Hispanic or Latino	11	3.7
Not Hispanic or Latino	241	80.3
Missing	48	16

Prior to disease onset, mean weight was 54.2 kg (*SD*=15.3), and individuals had lost an average of 11.3 kg (*SD*=9.7) before admission. During hospitalization, average weight gain was 1.8 kg (*SD*=1.5). Initial caloric prescription varied with a mean of 1714 kcal (*SD*=324.2).

Level of psychiatric functioning was obtained on admission and patients were screened using either the Global Assessment of Functioning (GAF) or the Children's Global Assessment Scale (CGAS). Two hundred and thirty individuals were scored using CGAS score, 59 with GAF score, and 11 with neither score. As the tools are scored on the same scale (0-100 points) and measure the same variable, they are reported here together. The average CGAS or GAF score on admission was 39.1 (*SD*=11.6, range 5-75). With regards to co-morbid psychiatric diagnoses, greater than 40% (41.7) of individuals were diagnosed with an anxiety disorder by the psychiatry consult team. Of those, 38% were classified as generalized anxiety disorder, 0.8% panic disorder, 0.8% post-traumatic stress disorder, 1.6% social anxiety disorder, 54% "Other" (unspecified anxiety disorder, adjustment disorder with mixed anxiety, anxiety disorder not otherwise specified), and 4% missing. See Table 3 for further summary of clinical characteristics.

Table 4.

Descriptive Characteristics of Sample

	N	%
Anorexia Nervosa Subtype		
Restricting	255	85
Binge/Purge	35	11.7
Atypical	6	2.0
Missing	4	1.3
Anxiety Disorder Diagnosis	126	41.7
Anxiety Disorder Subtype		
Generalized Anxiety Disorder	48	38
Panic Disorder	1	0.8
Post-Traumatic Stress Disorder	1	0.8
Social Anxiety Disorder	3	1.6
Other	68	54
Missing	5	4
	M (SD)	Range
Length of Stay	7.4 (5.9)	1-71
Admission		
Baseline Weight (kg)	42.8 (9.6)	17.4-75.6
BMI (kg/m^2)	16.3 (2.6)	10.1-25.5
%mBMI	82 (12.1)	52-139.3
Premorbid		
Weight (kg)	54.2 (15.3)	23.1-136.1
Weight Loss (kg)	11.3 (9.7)	-7.3-75.5
Weight Gain During Admission (kg)	1.8 (1.5)	-5.3-7
Initial Caloric Prescription (Kcal)	1714 (324.2)	1000-3000
CGAS or GAF Score	39.1 (11.6)	5-75
Phosphorous Nadir (mg/dL)	3.2 (0.6)	1.5-5.0
Day of hypophosphatemia	3.9 (3.4)	1-23

Eighty-six (28.7%) charts reported a phosphorus level of less than 3.0 mg/dL at some point during admission, making the rate of hypophosphatemia in this sample 28.7%. Mean day of hospitalization of first instance of hypophosphatemia was 3.9 (*SD*=3.4). The mean phosphorus nadir was 3.2 mg/dL (*SD*=0.6).

Factors Associated with Refeeding Hypophosphatemia (Question 1)

Prior to model building, the relationships between the independent variables and the dependent variable hypophosphatemia were examined using logistic regression and chi-square analyses (Table 5). Variables that were significantly associated with hypophosphatemia during admission and considered for the model included ever receiving nasogastric feeding ($p=.052$), %mBMI ($p=.019$), weight loss prior to admit ($p=.043$), age ($p=.001$), weight gain during admission ($p<.001$), potassium nadir ($p<.001$), magnesium nadir ($p=.001$), total formula in mL ($p=.026$), total formula in kcal ($p=.032$). Total dose of phosphorus was also significant ($p<.001$), but this was not included in the model because the variable measured total dose of phosphorus throughout hospitalization. Therefore, if a participant demonstrated hypophosphatemia, their supplemental dose of oral phosphorus would have been increased, making it likely that higher total doses of supplement would be associated with lower levels of serum phosphorus.

Correlations between variables considered for the model were examined using Pearson correlation matrix (see Table 6). Several associations were significant at the level of 0.01 or 0.05. Correlation coefficients were determined to be highly inter-correlated if $r > 0.70$. The relationship between total formula in mL and total formula in Kcal was highly inter-correlated, with $r=.99723$. Considering the greater clinical significance of total Kcal, the total formula in milliliters was removed from final model building and total formula in Kcal was retained. The remainder of relationships were not highly correlated; and therefore, retained in the analysis.

Table 5.

Variables Significantly Associated with Hypophosphatemia

	x^2	*p*
NG tube feeding	3.779	.041
	B	*p*
%mBMI	-.027	.019
Weight Loss Prior to Admit	.028	.043
Age at admission	.181	.001
Weight Gain	.409	<.001
Potassium Nadir	-1.876	<.001
Magnesium Nadir	-2.953	.001
Total Formula in mL	.000	.026
Total Formula in Kcal	.000	.032
Total Phosphorus Dose	.000	<.001

A logistic regression was performed to ascertain the effects of receiving NG feeding, admit %mBMI, weight loss prior to admit, age, weight gain during admission, potassium nadir, magnesium nadir, and formula in kcal on the likelihood of hypophosphatemia. Linearity of the continuous variables with respect to the logit of the dependent variable was assessed via the Box-Tidwell (1962) procedure. A Bonferroni correction was applied using seven factors in the model resulting in statistical significance accepted at $p<0.003125$. Using this significance level, all continuous independent variables were linearly related to the logit of the dependent variable and therefore included in the analysis. Five cases of studentized residuals greater than 2.5 standard

Table 6.

Pearson Correlations for Continuous Variables in Logistic Regression

	% Median Body Weight	Weight Gain During Admit	Weight Loss Prior to Admit	Potassium Nadir	Magnesium Nadir	Total Formula mL	Total Formula KCal	Age at Admit
%mBMI	1							
Weight Gain During Admit	-.350**	1						
Weight Loss During Admit	.078	-.002	1					
Potassium Nadir	.137*	-.192**	-.014	1				
Magnesium Nadir	-.008	-.046	-.163	.224	1			
Total Formula, mL	-.067	.334**	.025	-.159**	-.071	1		
Total Formula, Kcal	-.063	.323**	.022	-.149**	-.076	.997**	1	
Age at Admit	-.135*	.007	.264**	-.162**	-.250**	-.047	-.057	1

** significant at level of 0.01 (2-tailed)
*   significant at level of 0.05 (2-tailed)

deviations were revealed, all of which were kept in the analysis.

The logistic regression model was significant (x^2=59.3, p<0.001), and accounted for 21.9% (Cox & Snell R^2) to 31.0% (Nagelkerke R^2) of the variance, rejecting the null hypothesis that there is no association between factors identified in AYA with AN who develop RH and those who do not. Hosmer and Lemeshow test was not statistically significant (p=.445), indicating the data was a good fit to the model. A total of 76.7% of the cases of hypophosphatemia were correctly classified.

Of the independent variables, NG feeding (p=.054), age at admission (.022), weight gained during hospitalization (p=.003), potassium nadir (p=.001), and magnesium nadir (p=.024) contributed significantly to the model. Percent median body on admission, weight loss prior to admission, total formula in Kcal did not. Individuals who received NG feeding were found to have 3 times higher odds of hypophosphatemia. Increasing age was associated with 1.2 times higher likelihood, every kilogram of weight gain during hospitalization was associated with 1.5 times higher odds. Alternatively, for each unit reduction in potassium, the odds of hypophosphatemia increased by 9.2 and for each unit reduction in magnesium, the odds were 13.7 higher.

The regression model was performed two additional times. First excluding the outliers (those with studentized residuals greater than 2.5), and second excluding all individuals diagnosed with atypical anorexia nervosa (n=6). Like the model described above, NG feeding, %mBMI, weight loss prior to admission, age at admission, weight gain during hospitalization, potassium nadir, magnesium nadir, and total formula in both mL and kcal were associated with the outcome variable of hypophosphatemia. Excluding outliers, the final model included NG feeding (p=.056), age at admission (p=.016), weight gain during hospitalization (p=.002), potassium nadir (p=.002) and magnesium nadir (p=.022). The odds ratios remained the same as described above. Excluding individuals diagnosed with atypical anorexia, again the same variables were included in the final model, NG feeding (p=.023), age at admission (p=.011), weight gain during hospitalization (p=.005), potassium nadir (p<.001), and magnesium nadir (p=.050). Odds ratios remained the same as initial model. Thus, these two additional analyses did not reveal any new results.

To determine if there were statistically significant differences between those who received NG feeding and those who did not, chi-square analysis, t-tests, and logistic regression were performed. The two groups were not statistically significantly different at baseline assessment on sex, age on admission, BMI, %mBMI, premorbid weight, or weight loss prior to

Table 7.

Logistic Regression Predicting Likelihood of Hypophosphatemia Using All Factors Associated with the Outcome

	B	SE	Wald	df	p	Odds Ratio	95% CI
NG Feed Ever	1.078	.559	3.713	1	.054	2.937	.982-8.789
%mBMI	-.003	.015	.031	1	.861	.997	.968-1.028
Weight Loss Prior to Admit	.011	.018	.361	1	.548	1.011	.975-1.048
Age at Admit	.169	.074	.5.245	1	.022	1.184	1.025-1.368
Weight Gain During Admit	.427	.142	8.985	1	.003	1.533	1.159-2.2026
Potassium Nadir	-2.222	.671	10.958	1	.001	9.259	2.475-34.482
Magnesium Nadir	-2.622	1.164	5.080	1	.024	13.7	1.408-142.857
Total Formula in Kcal	.000	.000	.210	1	.647	1.000	.999-1.001

Constant 8.968

admission. Additionally, when considering factors significantly associated with hypophosphatemia, the two groups did not differ on weight gain during admission, potassium nadir, or magnesium nadir. However, the groups did have significant difference in starting caloric prescription, with those who received NG feeding receiving significantly more calories at the start of the admission and total calories of formula given with those who required NG feeding having significantly more formula over the course of admission (see Table 8).

Table 8.

Group differences Between Those Who Received NG Feeding vs. Those Who Did Not

	No NG Feeding M (SD)	NG Feeding M (SD)	*p*	Odds Ratio
Sex (female)			.852	.853
Age (years)	15.5 (2.4)	15.2 (2.8)	.444	.880
BMI (kg/m^2)	16.3 (2.6)	16.4 (2.9)	.784	1.191
%mBMI	81.9 (11.9)	83.3 (12.9)	.488	.989
Premorbid Weight (kg)	54.3 (13.9)	53.7 (23.3)	.855	.941
Weight Loss Prior to Admit (kg)	10.4 (8.7)	11.5 (16.1)	.551	1.106
Starting Kcal	1696.8 (311.3)	1817.1 (379.1)	.023*	1.002
Weight Gain During Admit (kg)	1.7 (1.42)	2.1 (1.76)	.091	.775
Potassium Nadir	3.7 (.31)	3.6 (.43)	.070	.778
Magnesium Nadir	2.0 (.15)	1.9 (.15)	.267	.509
Total Formula Received in Kcal	1554 (2553)	11210 (17437)	<.001*	1.000

Factors Associated with Phosphorus Nadir (Question 2)

Similar to Question 1, relationships between independent variable and the dependent variable serum phosphorus level were examined. Continuous independent variables were assessed using logistic regression, categorical independent variables were assessed using chi square to determine relationship with phosphorus nadir. Relationships were considered significant if they reached a p value of less than or equal to 0.05. Variables that were significantly associated with phosphorus nadir were bradycardia at night (p=.047), admit BMI (p=.030), overnight heart rate minimum (p=.025), magnesium nadir (p=.002), formula amount in kcal (p=.037) and anxiety disorder diagnosis subtype (p=.002). Also significant was total dose of phosphorus during admission (p<.001); however, this was not included in the model because it does not provide clinically pertinent information.

A multiple regression was used to test if the factors listed in Table 9 significantly predicted minimum serum phosphorus level. Partial regression plots and plot of studentized residuals against predicted values were examined to determine linearity. Durbin-Watson statistic was 2.135 indicating no meaningful serial correlation and independence of residuals. Visual inspection of studentized residuals versus unstandardized predicted values showed homoscedasticity. Multicollinearity diagnostics were examined using VIF and Tolerance, both values approached 1.0 in final model making multicollinearity among final model variables of less concern. One case showed a studentized deleted residual of -3.099, however there were no concerning leverage values (greater than 0.2) and no Cook's Distance greater than 1.0; therefore, all cases were kept in final analysis. Normality was assessed via Q-Q plot of studentized residuals.

Final model included admit BMI and magnesium nadir. The model was statistically significant $F\,(2,122) = 11.986$, $p<.001$, $R^2=.168$, meaning that 16.8% of the variance in phosphorus nadir is explained by the factors listed above, adjusted $R^2=.158$. Magnesium nadir contributed most to the model with $b=.324$ ($p<.001$), indicating for every 1-unit increase in magnesium results in 1.213 increase in phosphorus, followed BMI $b=.271$ ($p=.002$) with each point adding .060 increase in phosphorus.

Table 9.

Variables Significantly Associated with Phosphorus Nadir

	x^2	*p*
Bradycardia at night	45.3	.047
Anxiety Disorder Subtype	281.1	.002
	F	*p*
BMI	32.7	.030
Overnight heart rate nadir	1.5	.025
Magnesium Nadir	3.0	.002
Formula Amount in Kcal	1.4	.037
Total Dose of Phosphorus	4.2	<.001

Table 10.

Summary of multiple regression analysis

	B	SE_B	β
Intercept	-.135	.695	
BMI	.060	.019	.271*
Magnesium Nadir	1.213	.314	.324*

$^*p<.05$
B= unstandardized regression coefficient; SE_B= standard error of the coefficient;
β= standardized coefficient

Summary

This study sought to address two questions, specifically, what factors were associated with the outcome of hypophosphatemia and what factors were associated with a change in serum phosphorus level, regardless of whether that level went below the threshold for hypophosphatemia. A logistic regression was performed to address the first question. The findings suggest that individuals who received NG feeding, were older, gained more weight, and had other electrolyte abnormalities were at the greatest risk for developing hypophosphatemia. Multivariate regression analyses were used to determine what factors influence serum phosphorus level. This analysis suggested that lower weight on admission and other electrolyte abnormalities contributed variation to serum phosphorus level; however, the amount of variance attributed to these variables was low.

CHAPTER 5

Conclusion

The purpose of this study was to identify factors that contribute to the outcome of RH in a population of AYA admitted the hospital with AN. This study builds on prior knowledge of risk of RH described in the literature, and contributes unique knowledge of this outcome in the AYA population. This chapter reviews and discusses the results of this study, the limitations, and implications for nursing practice, education, research and policy.

Discussion

The sample was primarily female, white/Caucasian, and non-Hispanic, consistent with literature describing prevalence of AN in the population (Hoek & van Hoeken, 2003; Smink et al., 2012). The majority of the sample was adolescent, between the ages of 10-19 years with a mean age of 15.5. This coincides with the peak onset of AN (Swanson et al., 2011). AN-R, was reported as the most common subtype in this sample. Individuals had a compromised level of psychiatric functioning as measured by CGAS or GAF score, and a large portion of the sample had diagnosed anxiety disorder, similar to other studies that report high rates of comorbid anxiety in this population (Hudson et al., 2007; Swanson et al., 2011).

The logistic regression model to predict factors that are associated with RH in AYA included NG feeding, age at admission, weight gain during hospitalization, potassium and magnesium nadir. It is of clinical relevance that in this sample, NG feeding was associated with three times higher odds of RH. The meal-based protocol utilized in this population indicated that NG feeding was only provided in cases of food refusal or failure to complete meals. There is not a clear consensus in the literature on whether NG feeding itself or method of NG feeding as continuous or bolus nutrition is predictive of or protective against RH. Systematic and integrative reviews have found between 1-35% incidence of RH among individuals diagnosed with AN and fed via NG (Rizzo et al., 2018; Kells et al., 2016).

In this sample, differences between groups of those who received NG feeding and those who did not revealed that those who received NG feedings had a higher initial caloric prescription. This questions whether high starting calorie requirement was in some part related to the necessity of NG feeding due to patient inability to complete the volume of meals. It is also unclear if those who received NG feeding had a greater degree of starvation resulting in RH during admission. However, in comparing the two groups, those who received NG feeding did not have lower weight during admission, percent median body weight, BMI, or weight loss prior to admission, which argues against this supposition.

Traditionally, a lower caloric diet during hospitalization has been suggested to prevent RH and refeeding syndrome. However, higher caloric prescription at admission has been recommended to expedite weight gain and promote shorter duration of hospitalization (Garber et al., 2012), and has not been associated with poor outcomes (Garber et al., 2016; Garber et al., 2012; Whitelaw et al., 2010). Starting caloric prescription was not significantly associated with either hypophosphatemia or phosphorus nadir in this study. As the medical complications of AN are related to starvation as a result of the psychiatric profile of the disease, and treatment is focused on psychiatric care, the inpatient medical setting may not be of greatest utility for these individuals. Improving inpatient medical care to facilitate timelier discharge to needed psychiatric care would be of great clinical significance. The findings of this study would support higher caloric prescription on admission to promote reduced length of stay and transfer to appropriate psychiatric care.

For every year of age, likelihood of RH increased in this sample. The results show a 1.2 times higher likelihood of RH in older individuals. Previous studies have described poorer outcomes for individuals with older onset or age at initial assessment for AN (Ackard et al., 2014; Buhren et al., 2013; Wentz et al., 2012). Additionally, a longitudinal study reported that younger individuals had lower mortality rates supporting the theory of worse outcomes for older AYA with AN (Franko et al., 2013). Considering the peak incidence of AN occurs between 15-19 years of age (Wentz et al., 2012; Favaro et al., 2009), older age at assessment or treatment may be related to longer duration of illness (Franko et al., 2013). Identifying the difference between age as a predictor of RH versus longer duration of illness was not ascertained in this study. Future studies should include an assessment of illness duration in regards to incidence of RH.

The finding of older age on admission as a predictor of poorer outcomes in this study, in addition to previous studies reporting less favorable results for older individuals with AN (Ackard et al., 2014; Buhren et al., 2013; Wentz et al., 2012), underlines the demand to advance public health efforts to improve awareness and screening. Recent literature has identified primary care clinician discomfort, perceived lack of confidence, and lack of resources in the diagnosis and management of eating disorders in adolescents (Higgins & Cahn, 2018; Robinson, Boachie, & Lafrance, 2013). Improved primary care physician screening and referral to treatment earlier in disease trajectory and when individuals are younger could be of benefit in the prevention of RH.

Weight restoration is a primary goal of medical hospitalization for individuals with AN (AAP, 2003; ADA, 2001; APA, 2006; Golden et al., 2003). In this sample, every kilogram of weight gained during hospitalization was associated with 1.5 times higher odds of developing hypophosphatemia. This finding may be reflective of low weight on admission, given research that suggests that low BMI on admission was predictive of RH (O'Connor & Nicholls, 2013) in that those with lower weight on admission have more weight to gain during the refeeding process. This study did not examine the rate of weight gain; however, previous reports have found that rate of weight gain was not predictive of RH (Redgrave et al., 2015). Further investigation of the rate of weight gain among this population may be warranted.

The results suggest that low levels of serum potassium and magnesium predicted low serum phosphorus. This finding is consistent with literature that highlights the importance of electrolyte imbalances during refeeding syndrome (Brown et al., 2015; Fuentebella & Kerner, 2009; Kraft et al., 2005; Rio et al., 2012). This study revealed elevated odds ratios, and therefore, increased risks of RH in those participants who demonstrated hypokalemia as well as those with hypomagnesemia. There may be clinical value to further elucidate temporal relationships and nadir levels of potassium and magnesium to better predict and prevent RH in this population.

This study reported that scores on psychiatric functioning scales (GAF and CGAS) and diagnosis of anxiety were not significantly associated with RH. Although anxiety disorder subtype was significantly associated with nadir phosphorus level, it was not in the final model as a predictor of the outcome. Previous reports have outlined that higher anxiety levels were associated with higher rates of resting energy expenditure (REE) (Van Wymelbeke et al., 2004; Castellini et al., 2014). In this study, it was posited that higher levels of anxiety would result in lower serum phosphorus levels as mediated by higher resting energy expenditure. However, direct measurement of REE through indirect or direct calorimetry and measurement of anxiety level utilizing validated tools (such as the Hamilton Anxiety Rating Scale, Beck Anxiety

Inventory or others) were not obtained. These measurements should be considered in future prospective studies.

Multivariate analyses conducted revealed that BMI on admission and magnesium nadir levels contributed to variance in serum phosphorus levels, independent of the outcome of hypophosphatemia. Variance in serum phosphorus levels, without reaching the threshold of hypophosphatemia, may be clinically significant as clinicians may use dropping serum phosphorus levels to guide interventions such as dose of supplementation or use of prophylactic supplementation. The two predictors of variance in serum phosphorus have been reported in earlier studies. Low BMI on admission has been previously cited in the literature as a predictor RH in individuals with AN (O'Connor & Nicholls, 2013; Ornstein et al., 2003). Additionally, electrolyte abnormalities have been reported to occur concurrently with RH in refeeding syndrome (Fuentebella & Kerner, 2009; Kraft et al., 2005; Rio et al., 2012).

The development of RH appears to be multifactorial. Clinical scoring tools that consider multiple predictors of an outcome have been useful in a number of medical settings, including determination of acute appendicitis (Wagner, Tubre, & Asensio, 2018), predicting risk of cancer among hepatitis B carriers (Wong et al., 2010), and many others. Future research directed towards further identification of predictors and models that can accurately predict RH would be of great clinical utility. Research that could better predict RH may inform development of a clinical scoring tool similar to those found in other settings. Such clinical scoring tools for use in this population may guide clinicians with regards to caloric prescription, phosphorus supplementation, electrolyte monitoring, and risk stratification during inpatient care.

Limitations

This study is not without limitations, and findings presented should be interpreted with caution. First, retrospective studies are limited by the availability and existing documentation of variables. In this study, retrospective chart review was dependent on nursing, dietician, physician, and psychologist documentation that was variable, provider dependent, and sometimes incomplete. Documentation especially varied in free written progress notes by physicians, dieticians, and psychologists. For example, pre-morbid weight was at times reported in absolute terms, with regards to weight loss compared to previous weight, or not documented at all.

Variable selection was limited to that which was existing in the medical chart. Anxiety diagnosis and either GAF or CGAS score were used to explore the relationship between psychiatric distress and the outcome of hypophosphatemia; however, resting energy expenditure and anxiety level specific scoring were not available in this retrospective review.

Provider specific methods and reporting made identifying and classifying variables challenging. For example, in the case of anxiety disorder diagnosis, Anxiety Disorder NOS and Unspecified Anxiety Disorder were used in an interchangeable way across clinicians; however, it is unclear if these two categories capture the same target diagnosis. Intrinsic to the seven-year date range utilized in this study is variations in clinical practice, which influenced both documentation and procedures. This was seen with the use of the CGAS versus the GAF scoring tool to measure psychiatric functioning. In this timeframe, the GAF was used for all individuals prior to August 2012, after which time the CGAS was used by the psychiatry consultation team. Additionally, classification of AN was redefined with the release of the DSM-V in 2013. Subsequently, AN subtype and identification of AN cases may reflect these changes in persons admitted prior to 2013 and those admitted after publication date. The two changes to the definition of AN between DSM-IV and DSM-V includes the removal of amenorrhea and the criteria of being less than 85% of ideal body weight. Therefore, an individual diagnosed prior to the DSM-V release may have been classified as Eating Disorder Not Otherwise Specified (ED-NOS), while an individual with a similar profile diagnosed after 2013 may have been classified as AN.

The individuals included in this study may not be representative of all AYA diagnosed with AN. Although the primarily female, non-Hispanic white sample was congruent with literature reporting prevalence rates of AN, males and minority populations were underrepresented. There were no available data related to sexual or gender orientation. Gender dysphoria is an emerging topic within the field of eating disorders, with case reports of co-occurrence of the two reported (Ewan, Middleman, & Feldman, 2014; Hepp & Milos, 2002; Murray, Boon, & Toyz, 2013; Strandjord, Ng, & Rome, 2015), and increased interest in the complexities of treating individuals within that population. It remains unclear if gender identity influences severity of AN and, in turn, medical complications such as RH. Additionally, the setting was a single site in the northeastern part of the United States, which utilized a site-specific protocol for nutritional rehabilitation. Alternative feeding regimens, phosphorus supplementation, laboratory monitoring, psychiatric care plans and other aspects of inpatient medical hospitalization were not explored or compared in this current study.

Implications for Nursing Practice

This study incorporates the nursing paradigmatic perspectives of person and health and is consistent with nursing themes of inquiry of life processes for optimal human functioning described by Donaldson and Crowley (1978). This inquiry generated new knowledge on the relationship between factors that are associated with development of serum hypophosphatemia or variation in serum phosphorus level for AYA with AN. The findings may be used to identify risk and to inform interventions that include individualized care plans for individuals for prevention and management of RH, including appropriate phosphorous supplementation and nutritional protocols. As advocates for optimal patient care and key members of the clinical care team, nurses are uniquely situated to develop and implement such individualized care plans. Improved prevention and management of RH during medical admission may facilitate timelier transfer to needed psychiatric care for this population. Working to positively influence the health of individuals, group, and society is in accordance with the nursing's social contract (American Nurses Association [ANA], 2010) to provide the common "good" of health care within a diverse and global society.

Implications for Nursing Education

This study provides insight into the complex nature of treatment for AYA with AN, with nutritional, nursing, medical, and psychiatric care components. This highlights the need for interdisciplinary care team involvement. Nursing education that emphasizes understanding of complex physiologic systems and collaborative team-based approaches is imperative. Nursing education on the general aspects of care of individuals with AN is also of concern and must be addressed. Research suggests that improved understanding of care for individuals with AN and development of therapeutic relationship is challenging for nurses (Ramjan, 2004; Salzmann-Erikson & Dahlen, 2017) and that patients may respond more favorably to treatment approaches with improved nursing relationships (Salzmann-Erikson & Dahlen, 2017). Education on the complexities of treatment of AN may enable greater rapport between nurse and patient, resulting in more advantageous patient outcomes and nurse satisfaction in working with this challenging population.

Dissemination of research findings in settings that incorporate these key components of education should be pursued. Interdisciplinary and nursing focused clinical conferences, peer-reviewed journals, and development of AN focused curriculum would promote improved clinician understanding of care for this population and incorporate findings into clinical practice.

Implications for Nursing Policy

Given the complex bio-psycho-social nature of AN (SAHM, 2015), interdisciplinary collaboration with colleagues in the fields of psychiatry, nutrition, and medicine will be important to continue to improve care for AYA with AN. The Institute of Medicine (IOM) published a report envisioning the future of nursing (2010). In this report, the second recommendation is to “expand opportunities for nurses to lead and diffuse collaborative improvement efforts” (IOM, 2010, p. 11). Adolescent health, and in particular eating disorders in adolescence, requires collaborative efforts to solve the complex, multifaceted questions associated with healthcare for this population. Identification of risk factors associated with RH during nutritional restoration is one area in which interdisciplinary collaboration is imperative. This study begins to describe some potential considerations for identification of risk and prevention of RH and may be used to develop future policy to standardize and improve the care for AYA with AN.

Recommendations for Future Research

The ultimate goal of the nursing discipline is to enhance the health of individuals and society (ANA, 2010), and in conducting collaborative, interdisciplinary, multiple methods research healthcare scholars can elucidate knowledge for evidence-based practice (Woods &

Magyary, 2010). The overall results of this study provide information regarding the risk of RH; however, they do not fully capture the risk in this population. Together, predictors in the multivariate analyses accounted for only 16% of the variance in phosphorus nadir during medical admission in this population. This relatively low percentage of explained variance highlights the need for further investigation.

Other factors of RH should be explored to further identify risk, guide clinical practice, and improve patient care. Specifically, pH of body fluids was found to influence hypophosphatemia in individuals diagnosed with alcoholism (Gutierrez, 2017) and could be explored in AYA with AN. Physiologic functions that influence phosphorus absorption and excretion are of interest. Vitamin D has shown to play a role in the absorption of phosphorus in the gut (Boyle & Goldfarb, 2017; Hruska, 2017); therefore, serum vitamin D levels or vitamin D supplementation could be investigated in relationship to RH. PTH levels are known to influence phosphorus reabsorption in the renal tubules (Hruska, 2017), and could be included in future exploration of RH risk factors.

Illness trajectory is of interest with relation to RH, as Whitelaw et al. (2010) found that fewer admissions were associated with higher likelihood of RH. This is suggestive that RH is at higher risk earlier in the course of the disease, making early identification and intervention of an important consideration. Furthermore, AN is a chronic disease, with less than half of patients achieving full recovery, and up to 20% of individuals experiencing chronic AN (Steinhausen, 2009). As such, early versus later risk factors may influence management of the illness over time.

While there is some literature describing the experience of nasogastric tube feeding for individuals diagnosed with AN (Halse et al., 2005), little is known about the experience and meaning of nutritional restoration during hospitalization for this population. A mixed method study could be designed to further explore this phenomenon and the mind-body relationship between NG feeding meaning, anxiety or psychiatric distress, and serum phosphorus levels as mediated by resting energy expenditure.

Further inquiry into the intersection of nutritional status on admission and starting caloric prescription may be of interest. In the population reported in this research, starting caloric prescription was at dietician discretion and based on intake prior to admission. One could consider a comparison of development of RH among three groups whose starting caloric prescription is rooted in 1) weight on admission only 2) combination of weight on admission and intake prior and 3) intake prior to admission only. Additionally, rate of weight gain among groups may garner useful information for practice.

Further inquiry to refine the relationship between psychiatric state, resting energy expenditure, and RH is needed. A potential next step would be direct measurement of anxiety using validated anxiety scales in a prospective cohort. Additional investigation of common psychiatric co-morbid diagnoses, such as OCD and depression, was lacking in the present study and could be of important consideration.

Summary

Variations in clinical practice with regards to length of stay, phosphorus supplementation, use of NG feedings, and caloric prescription (Schwartz et al., 2008) are indicative of a need for more definitive research into what individual or cumulative factors lead to greatest chance of RH during the nutritional rehabilitation phase of treatment for AN. Results of this study advance the knowledge of the risk of development of RH or changes in serum phosphorus levels in this population. The factors identified provide insight into potential areas for monitoring and individualized care plans for the prevention and management of the outcome. Clinicians should consider use of NG feeding, weight gain during hospitalization, age on admission, and electrolyte values when evaluating frequency of phosphorus monitoring, use of phosphorus supplementation, and caloric prescription. However, the lack of robust predictive value of the model underscores the urgent need for further inquiry in this area. Areas of investigation with regards to feeding methods, mediators of phosphorus pathophysiology, and psychiatric status with regards to phosphorus levels in AYA with AN should be explored.

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Appendix A. Data Abstraction Forms

Confidential

Factors Associated with Refeeding Hypophosphatemia in Adolescents and Young Adults Hospitalized for Anorexia Nervosa

Inclusion/Exclusion Criteria

Study ID ________________________________

Age at Admission: ________________________________

(DOB: [dob] | Admit date: [admitdate])

Inclusion Criteria

	Yes	No
Age 10-24 years at time of admission	○	○
Admitted to 7West in target dates 2010-2016	○	○
Diagnosed with Anorexia Nervosa	○	○

Exclusion Criteria

	Yes	No
Age < 10 or greater than 24	○	○
Co-morbid bulimia nervosa, binge eating disorder, serious mental illness including schizophrenia, schizoaffective disorder	○	○
Medical Hospitalization within last 14 days	○	○
Feeding other than PO or NG	○	○

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Factors Associated with Refeeding Hypophosphatemia in Adolescents and Young Adults Hospitalized for Anorexia Nervosa

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Demographic Data

Study ID ______________________

DEMOGRAPHIC DATA

Medical Record Number ______________________

Date of Birth ______________________

Sex
- ◯ Male ◯ Female

Ethnicity
- ◯ Hispanic or Latino
- ◯ NOT Hispanic or Latino
- ◯ Unknown

Race
- ◯ White/Caucasian
- ◯ Black/African American
- ◯ Asian
- ◯ Pacific Islander or Native Hawaiian
- ◯ American Indian or Alaskan Native
- ◯ Other
- ◯ Unknown

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Factors Associated with Refeeding Hypophosphatemia in Adolescents and Young Adults Hospitalized for Anorexia Nervosa

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Baseline Data

Study ID	________________
Admission Date	________________
Discharge Date	________________
Premorbid Weight (kg)	________________
Admission Weight (kg)	________________
Baseline Weight (kg)	________________
Discharge weight (kg)	________________
Admission Height (cm)	________________
Admit BMI	________________
Calculated Admit BMI	________________
Median Body Weight	________________
Percent Median Body Weight on admission	________________
Anorexia Nervosa, Subtype	◯ Atypical anorexia nervosa ◯ Restricting ◯ Binge/Purge ◯ Avoidant/restrictive food intake disorder ◯ Purging ◯ Unspecified Feeding or Eating Disorder / Eating Disorder - NOS ◯ Other specified feeding or eating disorder ◯ Missing ◯ No subtype listed
Anorexia Nervosa, Subtype Full Text	________________
GAF Score on admission	________________

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Factors Associated with Refeeding Hypophosphatemia in Adolescents and Young Adults Hospitalized for Anorexia Nervosa

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Daily Data Log

Study ID	______________________
Date	______________________
'FINAL' date	______________________
Weight (kg)	______________________
Supine Heart Rate (bpm)	______________________
Standing HR (bpm)	______________________
Supine Systolic Blood Pressure (mm/Hg)	______________________
Supine Diastolic Blood Pressure	______________________
Standing Systolic Blood Pressure (mm/Hg)	______________________
Standing Diastolic Blood Pressure	______________________
Heart Rate 10 AM (bpm)	______________________
Heart Rate 2PM (bpm)	______________________
Heart Rate 6PM (bpm)	______________________
Heart Rate 10 PM (bpm)	______________________
Lowest Overnight HR (bpm) (lowest between 10pm - 6am)	______________________
Systolic Blood Pressure 10 AM (mm/Hg)	______________________
Diastolic Blood Pressure 10 AM (mm/Hg)	______________________