Self-reported Adherence and Beliefs towards Immunosuppressive Medications at Ahmed Gasim Kidney Transplantation Centre, Khartoum State, Sudan (2016)

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B. Pharm, Faculty of Pharmacy, University of Gezira (2004)

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Submitted to the University of Gezira in Partial Fulfillment of the Requirements for the Award of Master Degree in Pharmacy (M. Pharm)

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<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
<th>Signature</th>
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</thead>
<tbody>
<tr>
<td>Prof. Abdalla Omer Ahmed Elkhawad</td>
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<td></td>
</tr>
</tbody>
</table>

March, 2017
Self-reported Adherence and Beliefs towards Immunosuppressive Medications at *Ahmed Gasim* Kidney Transplantation Centre, Khartoum State, Sudan (2016)

Suha Abd Elmoniem Mohammed Ahmed

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<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
<th>Signature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prof. Abdalla Omer Ahmed Elkhawad.</td>
<td>Chair person</td>
<td></td>
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<tr>
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</tr>
</tbody>
</table>

March, 2017
Declaration:

I would like to declare that the dissertation entitled "Self-reported Adherence and Beliefs towards Immunosuppressants in Ahmed Gasim, Khartoum state, Sudan," submitted in partial fulfillment of requirement for the Award of the Degree of Master of Pharmacy (M.Pharm). Is may own work throughout nine month of continuous working and has not been submitted for any other previous studies.

Suha Abd Elmoniem Mohammed Ahmed
Dedication

To the loveliest parents who have always supporting me.
To my family members my husband, children, brothers.
This study could not been achieved without them.
Acknowledgment:

Pursuing a Master Degree is an exercise in patience, persistence, and perseverance. This completed research could not have been accomplished without the support and guidance of many individuals.

The warm welcome, genuine support, extended to me by the Ahmed Gasim Hospital Transplant Clinic staff and colleagues in the hospital pharmacy.

Special thanks for my supervisor Prof. Abdalla Ahmed Alkhawad Omer for facilitated appointments and sharing his big knowledge with me.

Thank you to Dr. Mohammed Osman Mohammed Elmustafa for the time spent in reviewing my research and the quality feedback provided to help enhance the quality of this research.

My husband Mr. Alfatih Mustafa Dafaallah for his continuous support and encouragement.

Understanding of quantitative and qualitative statistics owing to Mr. Mahir Eissa Mohammed thanks for him.

At the end, I am very grateful to those who participated and helped me to complete this study, specially Mrs. Arwa Ali.
Self-reported Adherence and Beliefs towards Immunosuppressive Medications at Ahmed Gasim Kidney Transplantation Centre, Khartoum State, Sudan (2016)

Suha Abd Elmoniem Mohamed Ahmed

Abstract

Although immunosuppressive therapy after organ transplantation is critical for long term outcomes, patients do not comply with their immunosuppressive treatment as much as might be expected. Nonadherence among Sudanese kidney transplant recipient has not previously been studied. Hence the aim of this study was to explore nonadherence and beliefs among Sudanese kidney transplant recipients by using self-report instrument. In the present cross sectional study 171 renal transplant recipients participated by replying to a questionnaire. Two validated instruments were included, one on beliefs about medicine (Beliefs about medicine questionnaire BMQ), the other on nonadherence (Immunosuppressant therapy adherence scale ITAS). Those completing the Immunosuppressant therapy adherence scale (ITAS) were classified as adherent to immunosuppressive therapy (IST) if their ITAS score were 12 and nonadherent if their score was less than 12. The relationship between the dichotomized ITAS scores and patient variables that are readily available such as sex, age, kidney donor type, education level and time since transplantation, was assessed. The relationship of ITAS scores to patients, clinical data (serum immunosuppressant concentration and serum creatinine) was also assessed from regular follow up cards. Only 38.6% were adherent to immunosuppressants, and the remaining 61.4% were nonadherent, forgetfulness was the main cause for nonadherence. Patient sex, serum immunosuppressant concentration, education level were unrelated to adherence. Compared with nonadherent patients, adherent patients tended to be younger, to have received their transplant more recently, and to be less likely to exhibit an increase in serum creatinine (SCr) concentration and to have kidney from living unrelated donor. For the BMQ the necessity scores were extremely high (mean score 24.3±2.066) while the scores for concern were low (mean score11.73±5.049). There was significant relationship between beliefs towards
immunosuppressant and adherence. In general nonadherence to immunosuppressants was high among Sudanese kidney transplant recipients.

Further studies using multiple, valid and reliable measures of adherence that involve larger samples are needed to detect risk factors for adherence.
تقييمات عن الالتزام بالتعليمات الدوائية والمعتقدات عن استعمال المثبطات المناعية لزارعي الكلى في

مركز أحمد قاسم

سها عبد المنعم محمد أحمد أبو يسي

ملخص الدراسة

على الرغم من أن العلاج بمثبطات المناعة بعد زرع الأعضاء أمر بالغ الأهمية لتحقيق نتائج على المدى الطويل، والمرضى لا يلتزموا بالتعليمات الدوائية بالقدر المطلوب والمتوقع. مدى الالتزام بالتعليمات الدوائية بين زارعي الكلى في السودان لم يسبق دراسته وبالتالي كان الهدف من هذه الدراسة استكشاف عدم الالتزام والمعتقدات بين زارعي الكلى السودانيين من خلال استخدام نموذج خاص لجمع البيانات من المرضى وكرت المتابعة الدوريه. شارك 171 زارع عن طريق ملئ الاستبيان الذي يضم قسمين الأول يقيس مدى الالتزام بالتعليمات الدوائية والثاني يقيس المعتقدات حول استعمال مثبطات المناعة، وبيانات المرضى التي تنتمي بسهولة مثل الجنس والعمر ومصدر الكلي المزروعه، تم تقييم مستوى التعليم والوقت المضطروبة الزراعه للمرضى والبيانات السريرية (تركيز الدواء ومستوي الكرياتينين في الدم). كانت نسبة المرضى الملتمسين بالتعليمات فقط 38.6%، وكانت 61.4% الفئة المتبقية غير ملتزمة، كان النسبة السبب الرئيسي لعدم الالتزام، وتوزيع المريضين في الدم، مستوى التعليم، الجنس لا علاقة لها بالالتزام بالتعليمات. مقارنة مع المرضى غير الملتمسين بالتعليمات الدوائية، المرضى الأكثر التزاما كانوا أصغر سنًا وأحدوا عمليات الزراعه الأولى الأخرى، وكونها أقل احتمالًا أن تظهر زيادة في تركيز الكرياتينين في الدم. بالنسبة للمتعقدات الدوائية كانت الغالبية العظمى من المرضى متمسكة بالحفاظ على استعمال الدواء اثراً من الفرق من استعماله. كان هناك علاقة ذات دلالة إحصائية بين المعتقدات نحو مثبطات المناعة والالتزام بالتعليمات الدوائية. بصورة عامه كانت نسبة عدم الالتزام بالتعليمات الدوائية لثبت المتعقدات المناعة بين زارعي الكلى في السودان مرتفع جداً.
**List of Contents:**

<table>
<thead>
<tr>
<th>Supervision committee</th>
<th>II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Examination Committee</td>
<td>III</td>
</tr>
<tr>
<td>Declaration</td>
<td>IV</td>
</tr>
<tr>
<td>Dedication</td>
<td>V</td>
</tr>
<tr>
<td>Acknowledgment</td>
<td>VI</td>
</tr>
<tr>
<td>English abstract</td>
<td>VII</td>
</tr>
<tr>
<td>Arabic abstract</td>
<td>VIII</td>
</tr>
<tr>
<td>List of Contents</td>
<td>IX</td>
</tr>
<tr>
<td>List of tables</td>
<td>XI</td>
</tr>
<tr>
<td>List of abbreviation</td>
<td>XII</td>
</tr>
</tbody>
</table>

**Chapter one: introduction**

1. Introduction                   2
   1.1 General introduction        2
      1.1.1 Kidney transplantation  2
      1.1.2 The purposes of immunosuppressive drugs  3
      1.1.3 Adherence              3
   1.2 Rationale of the study      5
   1.3 Objectives                 6
      1.3.1 General objectives    6
      1.3.2 Specific objectives   6

**Chapter two: Literature review**

2.1 Literature review            8
2.2 Prevalence of nonadherence to immunosuppressive treatment 13
2.3 Measurement of adherence     13
   2.3.1 Direct measurement      13
   2.3.2 Indirect measurement   14
2.4 Determinants of nonadherence 14
2.5 Nonadherence to immunosuppression and graft failure 17
Chapter three: Materials and Methods

3.1 Study area 19
3.2 Study population 19
3.3 Study design 19
3.4 pilot study 20
3.5 Statistical analysis 21
3.6 Ethical approval 21

Chapter four: Results

4.1 General characteristics of study population 23
4.2 Adherence to immunosuppressants 24
4.3 Scores on BMQ specific questionnaire 25
   4.3.1 Patients beliefs towards immunosuppressants 25
4.4 Association of patient characteristics with adherence 26
   4.4.1 Immunosuppressant attitudinal groups and self reported adherence 28

Chapter five: Discussion

5.1 General characteristics of the study patients 30
5.2 Adherence to immunosuppressants 30
5.3 Association of patient characteristics with adherence 31
5.4 Beliefs towards immunosuppressants and adherence 33

Chapter six: conclusion and Recommendation

6.1 Conclusion 36
6.2 Recommendation 37
References 38
Appendix 44
List of tables:

<table>
<thead>
<tr>
<th>Table Number</th>
<th>Table Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.1</td>
<td>General characteristics of the study population</td>
<td>23</td>
</tr>
<tr>
<td>4.2</td>
<td>Responses to ITAS questions</td>
<td>24</td>
</tr>
<tr>
<td>4.3</td>
<td>Adherence to immunosuppressants</td>
<td>25</td>
</tr>
<tr>
<td>4.4</td>
<td>Scores on BMQ specific</td>
<td>25</td>
</tr>
<tr>
<td>4.5</td>
<td>Attitudinal analysis beliefs about immunosuppressive</td>
<td>26</td>
</tr>
<tr>
<td>4.6</td>
<td>Association of patient characteristics with adherence</td>
<td>27</td>
</tr>
<tr>
<td>4.7</td>
<td>Belief groups and adherence</td>
<td>28</td>
</tr>
<tr>
<td>4.8</td>
<td>Comparison belief groups using Fisher test</td>
<td>28</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
<td></td>
</tr>
<tr>
<td>BMQ</td>
<td>Beliefs about medicine questionnaire.</td>
<td></td>
</tr>
<tr>
<td>ITAS</td>
<td>Immunosuppressant therapy adherence scale.</td>
<td></td>
</tr>
<tr>
<td>IST</td>
<td>Immunosuppressant therapy</td>
<td></td>
</tr>
<tr>
<td>CKD</td>
<td>Chronic kidney disease</td>
<td></td>
</tr>
<tr>
<td>RRT</td>
<td>Renal replacement therapy</td>
<td></td>
</tr>
<tr>
<td>ESRD</td>
<td>End stage renal disease</td>
<td></td>
</tr>
<tr>
<td>SCR</td>
<td>Serum creatinine</td>
<td></td>
</tr>
<tr>
<td>ISDs</td>
<td>Immunosuppressive drugs</td>
<td></td>
</tr>
<tr>
<td>HD</td>
<td>Hemodialysis</td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>Peritoneal dialysis</td>
<td></td>
</tr>
<tr>
<td>CNI</td>
<td>Calcineurin inhibitors</td>
<td></td>
</tr>
<tr>
<td>BAASIS</td>
<td>Basal assessment of adherence scale for immunosuppressive</td>
<td></td>
</tr>
<tr>
<td>SMAQ</td>
<td>Simplified medication adherence questionnaire</td>
<td></td>
</tr>
<tr>
<td>NA</td>
<td>Nonadherence</td>
<td></td>
</tr>
<tr>
<td>LSD</td>
<td>Least significant difference test</td>
<td></td>
</tr>
<tr>
<td>NCF</td>
<td>Necessity concern framework</td>
<td></td>
</tr>
</tbody>
</table>
Chapter One

Introduction
1. Introduction

Many solid organ transplant recipients do not take their immunosuppressant therapy (IST) as prescribed. Nonadherence to IST after transplantation is one of the leading causes of allograft rejection, graft loss, and death (Moreso, et al., 2014). Despite the serious consequences of IST nonadherence in renal transplantation, which include decreased quality of life, increased health care costs, need for dialysis, morbidity and mortality, reported nonadherence rates range from 5% to 68% (Chisom, et al., 2005). Efforts to encourage IST adherence are an important aspect of post transplant medical care.

1.1 Kidney transplantation

Chronic kidney disease (CKD), most commonly defined as persistent impaired kidney function, is a comorbid condition with multiple manifestations that is recognized as an important worldwide public health problem. The prevalence of CKD has increased over years. It is strongly related with ageing and is more prevalent among women and African Americans (Almeida, et al., 2013). Without proper care, CKD leads to complications of reduced kidney function, increased risk of cardiovascular disease and ultimately, kidney failure, the need of renal replacement therapy (RRT) (namely the end-stage renal disease) and death (Almeida, et al., 2013). As seen worldwide, the prevalence of ESRD has significantly increased in developing countries. The growing number of patients with ESRD will consume a greater proportion of healthcare budget (Alsharif, et al., 2010). Kidney transplantation is the treatment of choice for most patients with end-stage renal disease (ESRD), it reduces disability, improves kidney function and quality of life, it also provides greater life expectancy and is more cost-effective compared with dialysis (Evans, et al., 1995). Only seven countries in Sub Saharan Africa (SSA) including Sudan have renal transplantation program (Naicker, 2013). Renal transplantation in Sudan is from living donors and no cadaveric donation program is available. The first patient transplanted from a living donor in Sudan was in 1974 (Banaga, et al., 2015). Renal transplantation constitutes 28.4% of total Renal Replacement Therapy (RRT) in Sudan while hemodialysis (HD) and Peritoneal Dialysis PD represent 69% and 3% respectively (Obeid, et al., 2009).
1.2 The purposes of immunosuppressive drugs (ISDs):
ISDs are used in treatment of autoimmune diseases or diseases that are most likely of autoimmune origin (e.g. rheumatoid arthritis, myasthenia gravis, systemic lupus erythematosus) and treatment of some other non-autoimmune inflammatory diseases (eg. long term Allergic Asthma control) (Rathee, et al., 2012). Currently, immunosuppressive drugs are used for three purposes in transplantation (Coico and Sunshine, 2009):

1.2.1 **Induction therapy**:
It is used to suppress the immune system approximately two weeks pre transplantation to reduce the incidence of immediate rejection of the graft.

1.2.2 **Maintenance therapy**:
In order to ensure that the immune system is kept at bay to facilitate graft survival over time, combinations of synergistic ISDs are used to interfere with specific immune mechanisms (such as T-cell activation). Typically, doses of ISDs used in maintenance therapy are lower than in induction therapy to allow the immune system to function and to minimize the incidence of opportunistic infections.

1.2.3 **Specific treatments**:
In some cases, episodes of acute rejection may occur months or years after transplantation. ISDs are used in these situations, typically at dose levels similar to those used in induction therapy regimens.

In renal transplantation multiple classes of drugs are used in combination. Usually, steroids are administrated with calcineurin inhibitors (CNI) such as cyclosporine (CsA) or tacrolimus (TAC) and either proliferation signal inhibitors (TOR-I) such as sirolimus (SRL) and everolimus (EVL) or antimetabolites (AMETAB) such as azathioprine (AZA) or mycophenolate mofetil (MMF) (Almeida, et al., 2013).

1.3 **Adherence**
WHO defines adherence to long-term therapies as ”the extent to which a person’s behavior – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider (Brown and Bussell, 2011). Often, the term adherence and compliance are used interchangeably. However, their connotations are somewhat
different: adherence presumes the patient's agreement with the recommendations, whereas compliance implies patient passivity in taking doctor’s order, rather than actively collaborating in the treatment process (Steiner and Earnest, 2000).

According to clinical trials, many effective treatments exist for chronic diseases, however the outcomes in the real world are not as expected from these explanatory trials and lack of adherence to treatment is considered one of the major reasons (Alhewiti, 2014). It has been estimated that, in developed countries, patients with chronic medical illnesses adhere only 50% of the time to their medications, and it is believed that the problem is much higher in developing countries (Sabate, 2003). In an effort to better understand the underlying causes of patients’ medication-taking behaviors, researchers have differentiated between two types of non-adherence. Intentional nonadherence is an active decision on the part of patients to forego prescribed therapy. Unintentional nonadherence, on the other hand, is a passive process whereby patients fail to adhere to prescribing instructions through forgetfulness, carelessness, or circumstances out of their control. Patients can, and often do, exhibit both types of nonadherent behaviors (Gadkari and Mchorney, 2012). Both intentional and unintentional are found to be influenced by patient’s beliefs towards their medications. There is a plethora of literature that supports the association between patient’s beliefs toward medication and adherence, and it has been proposed that beliefs are the strongest predictors of adherence (Horne and Weinman, 1999). Furthermore, knowing beliefs is important, as they tend to be fixed over time unless an intervention is made. An intervention such as education has been proven to change beliefs and there is evidence that targeting patient’s specific beliefs improves adherence (Sharaf, 2010).
1.4 Rationale of the study:

Kidney transplant patients are required to take lifelong immunosuppressive medication to prevent graft rejection. One vital aspect is to empower the patient to cope with their lifelong medication and its possible side effects. Lack of empowerment and too many side effects might lead to nonadherence and so the risk of both acute and late acute rejection as well as increased graft loss. Beliefs and adherence about immunosuppressants were studied in different parts of the world, but till now, neither beliefs about treatment nor nonadherence in Sudanese kidney transplant patients has not been studied.
1.5 Objectives:

1.5.1 General objective:

The aim of this study was to explore adherence and beliefs towards immunosuppressants among kidney transplant recipients at Ahmed Grasim transplantation centre.

1.5.2 Specific objectives:

a) To determine demographic features of the study population.

b) To examine the relationship between the two BMQ specific subscales (beliefs measure tool) and adherence.

c) To examine the relationship between demographic variables, time post transplantation type of donor, and adherence.

d) To find out if there is an association between laboratory test results for serum creatinine (determinant of kidney function) and adherence.
Chapter Two
Literature Review
2. Literature Review:

2.1 literature survey

While medication adherence rates of 80% are often cited as acceptable across many illness categories, a consensus definition of what constitutes optimum adherence in adult renal transplant recipients remains elusive (Osterberg and Blaschke, 2005). This review contains many studies that used different tools for adherence measurement.

Self reported non-adherence and beliefs about medication among Swedish kidney transplant recipients was studied by Lennerling and Forsberg., (2012). 250 renal transplant recipients participated by replying to two questionnaires one on beliefs about medicine (the BMQ), the other on nonadherence (Basal assessment of adherence scale BAASIS). They found that only 46% never failed to follow the medical treatment with respect to taking the drugs, dosage or timing (>2 hrs from prescribed time). Timing was the most frequently reported deviation (48%). Forty seven patients (16%) failed taking at least one dose of the prescribed immunosuppressants during the past four weeks. Four individuals reduced the prescribed doses. Only one reported taking a ‘drug holiday’. As suggested by the BMQ constructors, the difference between the necessity and concern scores was also calculated (necessity concern differential), nine participants reported stronger concerns than necessities for immunosuppressive medication. The necessity scores were extremely high while the scores for concern were low. Risk behavior identified by the BAASIS had no association in risk attitudes as identified in the BMQ. The only factor relating to non-adherence was lack of social support (p=0.022).

In USA a cross sectional study in the Prevalence and correlates of medication nonadherence among kidney transplant recipients was done by Chislom, et al., (2013). 252 patients included in this study were 59.9% male, 27.0% Black, and at a median of 2.9 years post transplant. The majority of study participants reported excellent adherence 59.1% scored 12 out of 12, while 26.6% scored either a 10 or 11. The remaining 14.3% scored between 2 and 9 on the 12-point ITAS. Non-adherence was associated with higher perceived stress, anxiety, and depression.

Also a total of 63 KTPs treated at the Clinic of Nephrology, Clinical Centre Nis, Serbia, 60 participated in the study. Study was done by lalic, et al., (2014) for Immunosuppressive Medication Adherence by responding to the simplified medication adherence questionnaire (SMAQ). Adherence was observed in 43 (71.7%) patients, and only 17 (28.3%) did not follow
the prescribed therapy. They found that nonadherence of the whole study group of patients (according to the SMAQ item) was more common due to forgetfulness than to intentional nonadherence. The effects of age and gender on the rate of adherence to medication were also insignificant. With regard to the tacrolimus level, a significant difference was also found between the adherers and the nonadherers (6.30 ± 2.06 vs. 5.0 ± 1.52 ng/ml, p < 0.05).

Factors associated with adherence to immunosuppressant therapy (IST) in renal transplant recipients were studied in Georgia by Chisholm, et al., (2005). One hundred thirty-seven patients completed the ITAS. Eighty-nine patients (65%) were adherent to IST, and the remaining 48 (35%) were nonadherent. Patient sex was unrelated to adherence. Compared with nonadherent patients, adherent patients tended to be younger, to take cyclosporine, to have lower incomes, to have received their transplant more recently, to have targeted immunosuppressant concentrations, to have greater refill-based adherence rates, and to be less likely to exhibit an increase in SCr concentration (p < 0.05). There was no significant difference in the number of rejections between adherent and nonadherent patients.

Nivens and Thomas, (2009) studied Quantitative patterns of azathioprine adherence after Renal transplantation. Medication vials incorporating electronic monitor circuits in their caps. Compiled prospective data files on the azathioprine dosing patterns of 180 adult renal transplant recipients have been monitored up to 4 years. These patients followed a mean of 8.7 years post transplantation. Patients were divided into three groups by the medication doses missed during the first 6 months post transplant. These initial dosing patterns remained remarkably consistent up to 4 years. Patients (n=47) missing the most doses (≥5%) experienced earlier and more frequent acute rejection episodes (P=0.025). This group also demonstrated significantly longer interdose intervals (P=0.005), with more frequent (P<0.001) and longer (P<0.001) drug holidays. A patient subgroup with early declining medication adherence (n=23) experienced dramatically poorer outcomes, with significantly increased acute rejection (P<0.001), chronic rejection (P=0.034), graft loss before death (P<0.001), and death (P=0.04). In all tertiles there was a trend toward missing more medication over time.

recruited to a larger cross-sectional study comparing different measures of adherence. Health beliefs were measured using standardized questionnaire (Beliefs about Medicines Questionnaire). Transplant and demographic details were collected from the notes. Seven [12%, 95% confidence interval (CI) 4–20%] subjects missed at least 20% of days medication and 15 (26%, 15–37%) missed at least 10% of days. subjects held a relatively strong belief in the need for immunosuppressants (97%). Lower belief in the need for medication and having a transplant from a live donor were the major factors associated with non-adherence.

Constantiner and Cukor, (2011) studied barriers to immunosuppressive medication adherence in 94 kidney transplant recipients from a medical center in Brooklyn, New York. Transplant patients waited for their monthly medical appointment completed questionnaires relating to their adherence (ITAS), barriers to medication taking, and beliefs in their abilities to take their medication as prescribed. The sample reported an average ITAS score of 11.0 _ 2.4, suggesting nearly perfect immunosuppressive medication compliance. The particular barriers that were most associated with lower levels of adherence were too many doses per day, too many pills per dose, having to remember to take medication, perceived side effects of medication, skipping a dose to feel good, falling out of a daily routine, and being short of money.

In Switzerland Denhaerynck., (2008) studied the prevalence and risk factors for nonadherence used a convenience sample of 249 adult kidney transplant patients >1 year post-transplant. Nonadherence was monitored electronically using MEMS. Selected socioeconomic, therapy, patient, condition and healthcare team-related risk factors for nonadherence were assessed. Period prevalences were expressed as the percent of prescribed doses taken (taking adherence), the percent of correctly dosed days (dosing adherence), the percentage of inter-dose intervals not exceeding 25% of the prescribed interval (timing adherence), and the number of drug holidays per 100 days (no intake for > 48 h if once daily or for > 24 h if twice daily intake). He found that mean taking, dosing, timing adherence, and drug holidays were 98%, 96%, 93%, and 1.1 days, respectively. Nonadherence was associated with higher self-reported non-adherence and male gender and younger age.
Medication Adherence and beliefs in Patients Taking Immunosuppressants after Kidney Transplantation have been studied by Jung, et al., (2010) used total of 222 functioning kidney transplant recipients in a single center in Korean society. Medical records have been reviewed retrospectively. Among 197 patients, 113 (57.4%) were compliant to the immunosuppressive agents, and 84 (42.6%) recipients were non-compliant. Non compliant patients were significantly younger (P=0.004), highly educated (P=0.004), employed (P=0.005), more likely to live alone (P=0.035), and drank more (P=0.001) than the compliant patients. Regarding psychosocial factor, weak beliefs about the necessity of taking medications (P=0.001), strong beliefs about specific concerns related to medications (P=0.038), and low self efficacy (P=0.003) were identified in the non-compliant group compared with the compliant group.

In the Brazilian state of Santa Catarina a sample of 50 patients have been selected by Maissiat et al.,(2013) from electronic medical records of patients that were submitted to renal transplant during the period 2007 to 2009. These patients were reviewed for adherence using Morisky scale. It was observed that 76% of the patients were considered to be non-adherent to the immunosuppressive treatment. Among the patients considered as non-adherents to the immunosuppressive treatment, 62% mentioned that the nonadherence was unintentional, while 2% did not present any motivation regarding the failure to adhere to the treatment prescribed. Other patients demonstrated that they had both understanding and motivation.

Self reported adherence and perceptions for immunosuppressants also studied in Hamilton by Burger et al.,(2015). The self reported survey consisted of two validated questionnaires: Beliefs about Medicines Questionnaire (BMQ) and Immunosuppressant Therapy Adherence Instrument (ITAS), Pharmacy refill histories and information about immunosuppressant (tacrolimus/cyclosporine) dose changes and drug levels were also collected to corroborate patient self-reported medication adherence. 93.5% (N=73) participants reporting 100% adherence to their immunosuppressant medications (ITAS score=12). Participants reported an overall high BMQ necessity score (mean score: 22.3, N= 126) and an overall low BMQ concerns score (mean score: 13, N= 115). age and sex found no association between these variables and the self-reported ITAS score <12.
A Longitudinal, Correlational Study of Patterns, Potential Predictors, and Outcomes of Immunosuppressive Medication Adherence in 201 adult kidney transplant recipients was done by Russell et al., (2010) from three centers providing post-transplant care located in the Mid-Western and Mid-Southern United States. Electronic monitoring was conducted for 12 months using the Medication Event Monitoring System. Older age was the only demographic variable associated with medication non-adherence ($r = 0.25; p = 0.005$). There were no other significant differences when examining years since transplant ($p = 0.75$), number of medications prescribed ($p = 0.60$), When medication adherence scores were examined, 74 of 121, or 61% had a medication adherence score lower than 0.90 and 41% lower than 0.80. No association was found between medication adherence scores and gender ($n=120$, $\chi^2 (1) = 0.87$, $p = 0.35$), ethnicity ($n=121$, $\chi^2 (2) = 7.08$, $p = 0.07$), marital status ($n=119$, $\chi^2 (4) = 8.20$, $p = 0.15$), employment ($N=119$, $\chi^2 (4) = 7.33$, $p=0.20$), education ($n=117$, $\chi^2 (4) = 6.24$, $p = 0.18$) or days since transplantation.

An epidemiological cross-sectional multicenter study was carried out by Ortega, et al., (2013) to investigate satisfaction and adherence to immunosuppressants using renal recipients who had received a transplant 6-24 months before and were undergoing immunosuppressant therapy (IT). Sociodemographic and clinical variables registered were dosage, allograft functioning, number of medications and Patient adherence to IT was analyzed based on the detection of abnormal values of blood immunosuppressant levels (which could not be explained by clinical data and a specialist’s judgment regarding patients’ compliance. Data from 206 patients were collected (61.2% males with a mean age of 53.35 years). Regarding patient adherence, most of the patients (70.9%) were compliant according to the specialists. This proportion was very similar to the percentage of patients who had not presented abnormal values in immunosuppressant levels (68.9%). Nonadherence rates (29.1% and 31.1%) were found. Also regarding adherence to treatment (presence of abnormal levels of immunosuppressant in blood test), multivariate analyses highlighted that medical criteria of noncompliance, treatment convenience and total doses of medications were significantly related factors. Moreover, it seems that the sex of the patient could also be a variable of interest when coping with this lack of compliance. It was shown that nonadherence rates are related to the number of doses being taken.
2.2. Prevalence of Nonadherence (NA) to immunosuppressive treatment

Taking into consideration the limitations associated with different methods to assess NA and the different definitions employed across studies, in 2004 a systematic review on the frequency and impact of NA to immunosuppressive drugs after kidney transplantation estimated that the prevalence was 22% for cross-sectional studies (n=15) and 15% for cohort studies (n=10) (Butler, et al., 2004). Later on, in 2007, a total of 147 studies published between 1981 and 2005 on kidney, heart, liver, pancreas, and lung transplants were included in a meta-analysis. In this report, the largest proportion of studies focused on kidney transplants (49%) and included a total of 29,000 patients contributing to an observation of 88,000 persons per year. Across all types of transplants, the average NA to immunosuppressants was 19–25 cases per 100 persons per year. Rates varied significantly by transplant type being the highest in kidney transplant recipients (36 cases per 100 persons per year) and, interestingly, the prevalence in North America was much higher than that in Europe (33.4 vs 13.5 per 100 persons per year (Dew, et al., 2007).

2.3 Measurement of adherence

Evaluation of NA to treatment should include an assessment of the four dimensions of adherence: taking, timing, dosing, and drug holidays (Sabate, 2003). It is important to remark that in contrast to other chronically ill patient populations, even minor deviations from the prescribed regimen (ie, taking <98% of the tablets, taking drug holidays, or variability in timing of medication intake of >2 hr) have been associated with an increased risk of late acute rejection, graft loss, and poor kidney function (Fine, et al., 2009).

Assessment methods of NA can be classified as direct and indirect with advantages and disadvantages for each one offering different levels of sensitivity.

2.3.1 Direct measurement

Include observation of medication intake and biological assays to measure drug levels or drug metabolites in the blood or urine. Observation verifies adherence but requires direct patient clinician encounters and it is a non feasible approach to monitor chronic treatments. Drug monitoring reflects the patient’s consumption of immunosuppressive drugs, but results can be
influenced by the half-life of drugs, metabolic rates, and white coat adherence (ie, greater adherence before a clinical visit) (Moreso, et al., 2014).

2.3.2 Indirect measurement

Include patient self-reporting (surveys, questionnaires, and interviews), collateral reports from family members or clinicians, prescription fills, pill counts, and electronic monitoring. Patients often under report nonadherence, prescription refill rates fail to provide information related to characteristics of nonadherence, pill counts fail to consider multiple sources of medication; and electronic monitoring fails to prove ingestion (Hansen, et al., 2007). Electronic monitoring, frequently considered the gold standard measure of adherence, has limitations that challenge both internal and external measurement validity. Self reporting is inexpensive and feasible in most clinical settings, but it may be biased by honesty of the patient and his/her capacity to recall. A study comparing self-report adherence with electronic measurement concluded that self report adherence, conducted in the setting of a confidential interview, to be the better measure for detecting missed doses and erratic dose timing (Butler, et al., 2004). Despite its limitations, it has been one of the most commonly used methods to assess adherence and there are different validated questionnaires for this purpose (Moreso, et al., 2014).

To date, no measure of adherence (direct, indirect) has emerged as a gold standard. Currently, a combination of these measures is used to assess adherence behavior.

2.4 Determinants of nonadherence

Nonadherence can be considered as a phenomenon that emerges from the interplay of numerous influential factors, categorized into five groups: (i) socio-economic factors, (ii) patient related factors, (iii) condition or disease related factors, (iv) therapy or treatment related factors, and (v) health care system and health care team related factors Determinants from all categories except for health care system and health care team related factors have to a certain extent been studied in kidney transplant patients. (Sabate, 2003).

2.4.1 Socioeconomic factors

Socioeconomic factors, while relatively non modifiable in nature, have been the most widely studied factors within the adult renal transplant population. Consistent with global studies exploring predictive values of these factors (age, gender, race, income level, education) across
illness categories (Sabate, 2003), results have been inconsistent within the adult renal transplant population. The majority of studies conducted within the adult population consistently conclude younger age as being associated with nonadherence (Chisom, et al., 2005 and Denhaerynck, et al., 2007). A review conducted by (Denhaerynck, et al., 2005) suggested that studies failing to associate a younger age with nonadherence lacked a significant subsample of adolescents. Also study done by Russell et al revealed that nonadherence increases with age (Russell, et al., 2010). Studies exploring the association of educational level with adherence yielded similar conflicting results with no consistent association with IST nonadherence identified (Butler, et al., 2004, Russell et al., 2010). Socioeconomic status in terms of income level, socioeconomic class and employment status equally contribute to mixed results.

2.4.2 Patient related factors

Of greater interest to clinicians are the modifiable patient-related or condition-related factors influencing the origins of IST adherence behavior. Patient related factors refer to the resources, knowledge, attitudes, beliefs, perceptions and expectancies of the patient (Sabate, 2003). A perceived need for medication (health beliefs) was found to contribute to IST nonadherence in several studies (Butler, et al., 2004, Alhewiti, 2014).

Research examining the effect of social interactions (social networks, social support) on IST adherence is limited. Social network variables such as living alone and/or being unmarried have been found to be associated with nonadherence (Butler, et al., 2004, Lennerling and Forsberg, 2012). The effect of social support on IST adherence among organ transplant recipients varies across studies. A meta-analysis by (Dew, et al., 2007) found poorer social support in solid organ transplants (kidney, heart, liver, pancreas, kidney/pancreas and heart and lung) to be associated with significantly greater IST nonadherence though the effect size was weak.

2.4.3 Condition or disease related factors

Medications have to be taken indefinitely for many chronic illnesses, and adherence to such treatment regimens often declines significantly over time. This is especially true for chronic illnesses that have few or no symptoms e.g., high blood pressure, osteoporosis, and hyperlipidemia. Without symptoms, a person may not be motivated to adhere to a treatment regimen (Berger, et al., 2004). The condition or disease related variables depression has been
found to increase the risk of treatment of NA threefold among patient populations (Moreso, et al., 2015). Both retrospective and prospective studies of kidney graft recipients report an association between NA and depression.

2.4.4 Therapy or treatment related factors

One factor that has been linked to NA is the complexity of the treatment. For many chronic diseases, research has shown that adherence decreases as the complexity of the medication regimen increases (ie, the number of pills per dose and number of doses per day, the necessity to observe strict requirements related to the intake of food, and the existence of special requirements regarding fluid intake) (Sabate, 2003). The pharmaceutical industry has developed different medications for renal transplant patients aimed to simplify treatment and improve adherence. Noticeably, conflicting results were obtained with this approach. In the randomized multicenter controlled trial, to evaluate adherence between a tacrolimus once-daily regimen and a tacrolimus twice-daily regimen using an electronic monitor to document drug intake, patients allocated to the once-daily group take the prescribed number of daily doses more often than patients allocated to the twice-daily group (88.2% vs 78.8%) (Kuypers, et al., 2013).

2.4.5 Health care system and health care team related factors

The quality of the doctor-patient relationship is one of the most important health care system-related factors impacting adherence (Krueger, et al., 2005). A good relationship between the patient and health care provider, which features encouragement and reinforcement from the provider, has a positive impact on adherence (Krueger, et al., 2003). Poor provider communication concerning the benefits, instructions for use, and side effects of medications can also contribute to nonadherence, especially in older adults with memory problems (Vermiere, et al., 2001).
2.5 None adherence to immunosuppressants and graft failure

The requirement for continuous immunosuppressive treatment to avoid graft rejection is well known from the beginning of the transplantation history. Numerous studies showed the impact of NA causing rejection and graft loss. Utilizing electronic monitoring to measure azathioprine adherence during a 6-month period in 134 renal recipients demonstrated a significant correlation between adherence and rejection free survival in the first 6 months post transplant. These data indicated that NA occurs early post transplant and tends to increase over time post transplant. Early NA was correlated with late NA and subsequent adverse clinical events (Fine, et al., 2009). Lower compliance rates during the first 6 months were associated in a “dose-response” fashion with acute rejection and allograft loss. Declining compliance during the first 90 days was a strong risk factor for later acute rejection and allograft loss. All cohort studies showed an increased risk of graft failure in nonadherent patients. Even with the use of measures generally accepted to lack sensitivity for the detection of NA, the odds of graft loss are increased about sevenfold in nonadherent patients when compared with adherent patients (Moreso, et al., 2015).

The link between chronic rejection, graft failure, and NA was well established in the observational study conducted by the Edmonton group including 315 transplant recipients who underwent a graft biopsy for cause. During follow up, 60 patients experienced graft failure. In this study, NA was only recorded retrospectively by medical chart review, based on records of patient admission or strong clinical suspicion by the attending clinicians. Concerns about NA were recorded 10 times more frequently in patients whose graft subsequently failed (32%) than in those whose grafts have not failed (3%), and nonadherent patients had donor-specific antibodies more often than did adherent patients.( Sellares, 2012).
Chapter Three
Materials and Methods
3- Material and methods:

3.1 Study area:
This study was conducted at Ahmed Gasim transplantation centre, Khartoum state, Sudan. It contains the largest organ transplant centre in Sudan where renal transplant patients attend the clinic every three month for follow up. Also, the centre has the only pharmacy that dispenses free immunosuppressants for renal transplant patients in Sudan.

3.2 Study population:
The study population consisted of a convenience sample of eligible adult renal transplant recipients who attended follow up clinics during January and March 2016. Consenting patients who were on immunosuppressants for more than one year, who were not known to have cognitive impairment or psychiatric illness, aged 18 years or older, having functioning kidneys were considered initially eligible for the study. Patients who received a second transplant or depended on others for medication management were excluded from the study.

3.3 Study design
A cross-sectional questionnaire based survey was conducted on patients who visited the follow up clinic during the period of study. All data were collected using the same questionnaire which included three parts described below:

3.3.1 demographics and clinical particulars of included patients these included:
- Sociodemographics and clinical particulars of included patients
  These included; patients age at the time of study, post transplant duration at time of inclusion, gender and education level.
- Serum creatinine level, as reported on the day of enrollment was obtained from the medical record. Serum creatinine values were then evaluated using transplant clinic normal values (0.4-1.4 mg / dL).

- Serum drug assays were obtained from medical records and evaluated according to target therapeutic values determined by the transplant clinic for recipients beyond the first year
from transplantation. The normal ranges were 100-150 ng/ml for Cyclosporine and 5-7 ng/ml for Tacrolimus.

3.3.2 Measurement of adherence used Immunosuppressant Therapy Adherence Scale (ITAS)

ITAS is a four-item, valid, reliable self-report measure that was developed to assess transplant recipients' immunosuppressant therapy (IST) adherence by asking them to indicate how often they were nonadherent to IST. Given a particular circumstance, questions asked to respondents were how often they (1) forgot to take their IST medications, (2) were careless about taking their IST medications, (3) stopped taking their IST medications because they felt worse, and (4) missed taking their IST medications for any reason. Response options are (3) 0% of the time, (2) 1–20%, (1) 21–50%, and (0) greater than 50%. Because this study measured adherence by only self reported method the number of patients response with a particular statement was assessed by categorizing the Likert scale responses as follows: (3) none of the time, (2) sometimes, (1) often, (0) very frequent. The ITAS has been found to have positive correlations with immunosuppressant refill based adherence rates and targeted serum immunosuppressant concentrations ($p < 0.01$). ITAS item scores were negatively related to rejection occurrence and increased SCr level ($p < 0.05$). (Chisholm, et al., 2005). ITAS has acceptable reliability and validity among solid organ transplant recipients.

3.3.3 Measurement of beliefs using beliefs about medicine questionnaire BMQ-specific

The Beliefs about Medicine Questionnaire (BMQ) was published by Horne et al., in 1999. The BMQ was built on the theoretical framework that adherence decisions are influenced by a cost-benefit assessment. The BMQ Specific comprises two scales: one assessing patients' beliefs about the necessity of preventer medication for maintaining present and future health (Necessity scale), and the other assessing their concerns about the potential adverse consequences of using it (Concerns scale). Each scale has core questions assessing beliefs (5 for necessity and 5 for concerns). Examples of questions from the Necessity scale are My health, at present, depends on my immunosuppressants and My health in the future will depend on my immunosuppressants. A questions from the Concerns scale is, I sometimes worry about the long-term effects of my medications, my medicines disrupt my life, All items are rated on a 5-point Likert scale as follows: 4 (agree) and 5 (strongly agree) were considered as agreeing; 1 (strongly disagree) and 2 (disagree) were considered as not agreeing. The separate Necessity and Concern scales were split at the scale midpoint to create four attitudinal groups (beliefs measure):
a) Skeptical (low necessity, high concerns).
b) Indifferent (low necessity, low concerns).
c) Ambivalent (high necessity, high concerns).
d) Accepting (high necessity, low concerns). (Horne, et al., 2008).

3.4 Pilot study:
The study instrument was piloted on 10 patients who were on ISDs in order to test the validity and reliability of the questionnaire used.

3.5 Statistical analysis:
Statistical analysis was done using the statistical package for social sciences (SPSS), version 20. Relationship between participant variables and adherence done by using Chi-square test, In comparing patient attitudes, an analysis of variance (ANOVA) used, P values less than or equal to 0.05 were considered as statistically significant and confidence level was 95%. Descriptive results were formulated as frequency and percentages.

3.6 Ethical Approval:
Ethical approval for this study has been obtained from the ethical committee in Ahmed Grasim hospital and the Khartoum State Ministry of Health.
Chapter Four
Results
4. Results:

4.1- General characteristics of the study population

One hundred seventy one completed the ITAS and BMQ questionnaire. The study population had a mean ± S.D age of 42.08±12.23 years also it was found that 124(72.5%) were males, 47(27.5%) were females, had a mean ± S.D time post transplantation of 4.81±3.540 years, 116(67.8%) received kidney from living related donor, 55(32.2%) received from un related donor and no one received kidney from deceased ones, highly educated patients (university and postgraduate) were 32.7% and 5.3% respectively, the largest number were in secondary school level 66(38.6%), the primary level 30(17.5%) and 10(5.8%) were illiterate as shown in table 4.1.

Table 4.1: general characteristics of the study population, n=171

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in yrs (mean± S.D)</td>
<td>42.08±12.23</td>
</tr>
<tr>
<td>Age [n (%)]</td>
<td></td>
</tr>
<tr>
<td>18-28</td>
<td>25(14.6%)</td>
</tr>
<tr>
<td>29-39</td>
<td>51(29.8%)</td>
</tr>
<tr>
<td>40-50</td>
<td>51(29.8%)</td>
</tr>
<tr>
<td>51-61</td>
<td>34(19.9%)</td>
</tr>
<tr>
<td>More than 61</td>
<td>10(5.8%)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>124(72.5%)</td>
</tr>
<tr>
<td>female</td>
<td>47(27.5%)</td>
</tr>
<tr>
<td>Time post transplantation in yrs (mean± S.D)</td>
<td>4.81±3.540</td>
</tr>
<tr>
<td>Type of donor</td>
<td></td>
</tr>
<tr>
<td>Living related</td>
<td>116(67.8%)</td>
</tr>
<tr>
<td>Living un related</td>
<td>55(32.2%)</td>
</tr>
<tr>
<td>Deceased</td>
<td>0</td>
</tr>
<tr>
<td>Education level</td>
<td></td>
</tr>
<tr>
<td>Illiterate</td>
<td>10(5.8%)</td>
</tr>
<tr>
<td>Primary</td>
<td>30(17.5%)</td>
</tr>
<tr>
<td>Secondary</td>
<td>66(38.6)</td>
</tr>
<tr>
<td>University</td>
<td>56(32.7%)</td>
</tr>
<tr>
<td>Postgraduate</td>
<td>9(5.3%)</td>
</tr>
</tbody>
</table>
4.2 Adherence to immunosuppressants

66 (38.6%) of the patients had a composite ITAS score of 12 and therefore were considered adherent, the remaining 105 patients (61.4%) had a composite score of less than 12 and were considered nonadherent. ITAS had a mean ± S.D score 10.62±1.602 as shown in table 4.3. Table 4.2 summarizes patients’ responses to the ITAS questions. The main reason of non adherence was the forgetfulness 166 (97.1%), 148(68.5%) was for reasons other than those included in this scale, 102(59.6%) of the patients nonadhered due to carelessness and finally 85(49.7%) due to they felt worse and experiencing side effects from their medication.

Table 4.2: Responses to ITAS questions, n=171

<table>
<thead>
<tr>
<th>Questions and response</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>In the last 3 months, how often did you forget to take your immunosuppressant medication?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>none of time</td>
<td>18</td>
<td>10.5</td>
</tr>
<tr>
<td>some times</td>
<td>48</td>
<td>28.1</td>
</tr>
<tr>
<td>often</td>
<td>166</td>
<td>97.1</td>
</tr>
<tr>
<td>very frequent</td>
<td>3</td>
<td>1.8</td>
</tr>
<tr>
<td>In the last 3 months, how often were you careless about taking your immunosuppressant medication?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>none of time</td>
<td>13</td>
<td>7.6</td>
</tr>
<tr>
<td>some times</td>
<td>71</td>
<td>41.5</td>
</tr>
<tr>
<td>often</td>
<td>102</td>
<td>59.6</td>
</tr>
<tr>
<td>very frequent</td>
<td>2</td>
<td>1.2</td>
</tr>
<tr>
<td>In the last 3 months, how often did you stop taking your immunosuppressant medication because you felt worse?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>none of time</td>
<td>1</td>
<td>0.6</td>
</tr>
<tr>
<td>some times</td>
<td>4</td>
<td>2.3</td>
</tr>
<tr>
<td>often</td>
<td>85</td>
<td>49.7</td>
</tr>
<tr>
<td>very frequent</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>In the last 3 months, how often did you miss taking your immunosuppressant medication for any reason?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>none of time</td>
<td>3</td>
<td>1.8</td>
</tr>
<tr>
<td>some times</td>
<td>20</td>
<td>11.7</td>
</tr>
<tr>
<td>often</td>
<td>148</td>
<td>68.5</td>
</tr>
<tr>
<td>very frequent</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Table 4.3: adherence to immunosuppressants, n=171

<table>
<thead>
<tr>
<th>patients</th>
<th>Frequency</th>
<th>Percent</th>
<th>Mean score± S.D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adhered (ITAS score,12)</td>
<td>66</td>
<td>38.6</td>
<td>10.62±1.602</td>
</tr>
<tr>
<td>Not adhered (ITAS score&lt;12)</td>
<td>105</td>
<td>61.4</td>
<td></td>
</tr>
</tbody>
</table>

4.3 Scores on BMQ specific questionnaire

As shown in Table 4.4 almost all the sample 98.2% had strong beliefs about the necessity of taking their immunosuppressant medications (scores above the scale midpoint and 24.3±20.66 mean score ) and only 22.2% reported high concerns about potential adverse effects , the mean score for concerns was very low 11.73±5.049 indicated that weak beliefs about concerns scale. The mean for necessity–concerns differential was 12.57± 5.6. Most of patients(98.8%) had necessity scores that higher than concerns scores (positive values for the necessity–concerns differential).

Table 4.4: scores on BMQ specific (comprising the Necessity and Concerns scales)

<table>
<thead>
<tr>
<th>Scales of BMQ-specific</th>
<th>Range</th>
<th>Mean</th>
<th>Std. Deviation</th>
<th>% Scoring above the scale midpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Necessity</td>
<td>5 to 25</td>
<td>24.3</td>
<td>2.066</td>
<td>98.2</td>
</tr>
<tr>
<td>Concerns</td>
<td>5 to 25</td>
<td>11.73</td>
<td>5.049</td>
<td>22.2</td>
</tr>
<tr>
<td>Necessity-concern</td>
<td>-20 to20</td>
<td>12.57</td>
<td>5.648</td>
<td>98.8</td>
</tr>
</tbody>
</table>

4.3.1 Patients beliefs towards immunosuppressants

The separate Necessity and Concern scales were split at the scale midpoint 15 to create four attitudinal groups. As shown in table 4.5 126 (73%) of patients accepted their treatments (high necessity, low concerns) which they had necessity score>15 and concerns score≤15 , 44(26.4%) were Ambivalent (high necessity, high concerns) which had score >15 on both scales. The smallest groups of patients were Indifferent (0.6%, low necessity, low concerns), they had score <15 on necessity,≤15 on concerns finally no one in Skeptical ( low necessity, high concerns) that had <15 scores on the necessity scale , ≥15 on concerns.
Table 4.5 attitudinal analyses of beliefs about immunosuppressive

<table>
<thead>
<tr>
<th>Groups</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indifferent</td>
<td>1</td>
<td>0.6</td>
</tr>
<tr>
<td>Skeptical</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Accepting</td>
<td>126</td>
<td>73</td>
</tr>
<tr>
<td>Ambivalent</td>
<td>44</td>
<td>26.4</td>
</tr>
</tbody>
</table>

4.4 Association of Patient Characteristics with Adherence

Women were no more likely to be adherent than men P 0.961 as shown in table 4.6, Compared with nonadherent patients, adherent patients were significantly younger P 0.044, had received their transplants more recently P 0.001, less often exhibited a rise in SCr concentration (to greater than 1.4mg/dl P 0.049 and received kidney from living related donor P 0.002. Serum immunosuppressant level for cyclosporine and tacrolimus were statistically unrelated to adherence P 0.138, 0.653 respectively, serum level of immunosuppressants for 48 patients that take tacrolimus (n=138) and 8 (n=31) patients from those take cyclosporine were unknown. Education level was significantly unrelated to adherence (P 0.116).
Table 4.6 Association of Patient Characteristics with Adherence, n=171

<table>
<thead>
<tr>
<th>variable</th>
<th>Adhered</th>
<th>Not adhered</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>48</td>
<td>76</td>
<td>0.961</td>
</tr>
<tr>
<td>Female</td>
<td>18</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 to 28</td>
<td>11</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>29 to 39</td>
<td>20</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>40 to 50</td>
<td>19</td>
<td>32</td>
<td>0.044</td>
</tr>
<tr>
<td>51 to 61</td>
<td>13</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>More than 61</td>
<td>3</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Time post transplantation (mean ±S.D)</td>
<td>2.18±0.389</td>
<td>2.41±0.494</td>
<td>0.001</td>
</tr>
<tr>
<td>Serum immunosuppressant concentration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclosporine:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Therapeutic range</td>
<td>4</td>
<td>12</td>
<td>0.138</td>
</tr>
<tr>
<td>Out of therapeutic range</td>
<td>5</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Un known</td>
<td>2</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Tacrolimus:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Therapeutic range</td>
<td>16</td>
<td>28</td>
<td>0.653</td>
</tr>
<tr>
<td>Out of therapeutic range</td>
<td>20</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Un known</td>
<td>18</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Serum creatinine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal level</td>
<td>62</td>
<td>88</td>
<td>0.049</td>
</tr>
<tr>
<td>Above the normal level</td>
<td>4</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Donor type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Living related</td>
<td>54</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>Living un related</td>
<td>12</td>
<td>43</td>
<td>0.002</td>
</tr>
<tr>
<td>Deceased</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Education level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Illiterate</td>
<td>7</td>
<td>3</td>
<td>0.116</td>
</tr>
<tr>
<td>Primary</td>
<td>10</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Secondary</td>
<td>26</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>University</td>
<td>22</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>Postgraduate</td>
<td>1</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>
4.4.1 Immunosuppressant attitudinal groups and self-reported adherence

An ANOVA comparison of multiple groups indicated that self-reported adherence differed significantly between groups as shown in table 4.7. Fisher's least significant difference test (LSD) indicated that the mean for adherence differ inside the belief groups. Accepting and Ambivalent groups showed higher adherence than Indifferent, mean difference were -4.240 and -3.878 respectively as shown in table 4.8. Accepting group reported the highest adherence between all groups. Indifferent group had the lowest adherence. There was insignificant difference in adherence between Accepting and Ambivalent groups.

<table>
<thead>
<tr>
<th>Adherence</th>
<th>Comparing groups</th>
<th>Sum of Squares</th>
<th>Mean Square</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between Groups</td>
<td>37.998</td>
<td>18.999</td>
<td>0.00001</td>
<td></td>
</tr>
<tr>
<td>Within Groups</td>
<td>396.378</td>
<td>2.374</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>434.376</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4.8 comparison between belief groups using Fisher's Least significant difference test (LSD)

<table>
<thead>
<tr>
<th>Adherence</th>
<th>Comparing groups</th>
<th>Mean Difference</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indifferent</td>
<td>Accepting</td>
<td>-4.240</td>
<td>0.00001</td>
</tr>
<tr>
<td>Accepting</td>
<td>Indifferent</td>
<td>4.240</td>
<td>0.00001</td>
</tr>
<tr>
<td>Ambivalent</td>
<td>Indifferent</td>
<td>3.878</td>
<td>0.001</td>
</tr>
<tr>
<td>Ambivalent</td>
<td>Accepting</td>
<td>-0.362</td>
<td>0.209</td>
</tr>
</tbody>
</table>
Chapter Five
Discussion
5. Discussion

5.1 general characteristics of the study patients

In this study the mean age of participants was 42.08±12.23 year, it was reported that GFR declines usually beginning after 30–40 years of age, the rate of decline may accelerate after age 50–60 years. This is due to multiple chronic diseases that affected the kidney of elderly population such as hypertension, diabetes mellitus and atherosclerosis, or other reasons of age related morphological changes in the renal system (Glassock and Winearls, 2009).

The present data showed the number of the males 124(72.5%) and the females 47(27.5%). This agreed with studies reported that male exhibit a more rapid age-related decline in renal function than female and several renal diseases appear to be gender-dependent (Neugarten, et al., 2000). A role for sex hormones to induce renal damage stems from studies in which aging male animals develop proteinuria and glomerulosclerosis, where as female and estrogen treated males are resistant to disease progression. There is previously published evidence that male gender is associated with a more rapid rate of progression of nondiabetic chronic renal disease (Neugarten and Golestaneh, 2013).

5.2 adherence to immunosuppressants

ITAS scale measured the forgetfulness, carelessness and intentionally stops taking their ISD because they felt worse which they are the 3 dimensions of non adherence over a 3 month time period. A time period of 3 months was selected given that patients’ recall of adherence is limited and decreases over time, and 3 months is often adequate to observe patterns of adherence to chronic medications such as IST (Chislom, et al., 2005).

Classification of patients according to ITAS score is controversial, some studies classified individuals who reported 11 or 12 in ITAS score as nearly perfect adherence and less than nearly perfect adherence (10 on the ITAS) (Constantiner and cukor., 2011). Their sample reported an average ITAS score of 11.0 ± 2.4, suggested nearly perfect immunosuppressive medication compliance. Others reported perfect adherence when patients score was 12, 10-11 was near
perfect and non adherence was identified as ITAS score≤9 (Chislom, et al., 2013), they found 59.1% scored perfect 12, 26.6% scored 10–11, and 14.3% scored 0–9. Chislom, et al., 2005 studied the relationship of ITAS scores to patients’ clinical and pharmacy data (e.g., graft rejection, serum IST concentrations, serum creatinine [SCr] concentrations, and pharmacy refill-based adherence rates), he classified participants into adherent (ITAS score=12) and non adherent (ITAS score<12) to avoid the bias.

In this study the percentage of patients who were classified as adherent to IST by ITAS composite scores was 38.6% and the percentage classified as non adherent was 61.4% as shown in Table 4.3, this agreed with that reported by Maissiat, et al., (2013) who used self reported tool of measurement (Morisky scale) and found that 76% of his participants were non adherent and disagreed with study that was done by Chislom, et al., (2005) who found that 65% of participants were adherent. The mean adherence score in this study was 10.62±1.602 suggested nearly perfect immunosuppressive adherence comparing with the study of Chislom, et al., 2013. Depending on which adherence measure was used, this study support important point that there was a high percentage of IST nonadherences existed among renal transplant recipients.

### 5.3 Association of patient’s characteristics with adherence

To assess the association of adherence with patient-specific factors, it was important for us to select a limited number of factors that were easily accessible for study, believed to influence adherence, and consistent (i.e., not changing dramatically over time) Chislom, et al., (2005). This study confirms the findings of some IST adherence studies but was indirect conflicted with others in term of factors associated with adherence. Study found that younger patients were more adherent than older patients, which agreed with results that found by Chislom, et al., (2005), Denhaerynk, et al., (2007) and Jung, et al., (2010). It makes sense that older adults would be less adherent than younger adults, given the probability of older patients having additional challenges, such as forgetfulness, increased impairment due to other conditions, and less access to health care (e.g., limited transportation).

Study also found recent transplantees which had (2.41±0.494) mean± SD years of transplantation to be more adherent than those who had transplants longer which conflicted with study done by Russel, et al., (2010).
Although Ortega, et al., (2013) and Denhaerynck, et al., (2007) confirmed the relationship of sex with adherence, this study failed to confirm this result and it was agreed with many studies done by Russel, et al., (2010), Chislom, et al., (2005) and Burger, et al., (2015). Although increased SCr concentrations can often result from IST non-adherence (e.g., in patients with rejection due to non-adherence), other events can also be responsible (e.g., dehydration, graft rejection due to reasons other than IST non-adherence) (Moreso, et al., 2014). Since SCr concentration is a clinical measure frequently used to assess renal function, it was used as such in this study, and it found that there was significant difference in scr concentration between adherent and non-adherent participants, adherent patients less likely to exhibit an increase in the concentration of serum creatinine this agreed with study done by Chislom, et al., (2005).

This study was failed to found the relation between levels of immunosuppressants and adherence which was found by study done by Ortega, et al., (2013), Lalic, et al.,(2014) who confirmed association between tacrolimus level and adherence and Chislom, et al., (2005) who found association between cyclosporine level and adherence. Cyclosporine and tacrolimus were the only immunosuppressant agents examined, because:
(1) They are commonly used (most renal transplant recipients are prescribed either cyclosporine or tacrolimus as their base IST).

(2) Blood concentrations of these agents are routinely measured in practice, thereby providing data to support adherence.

(3) Cyclosporine and tacrolimus are not used in the same regimen, since they are both calcineurin inhibitors and inhibit the calcineurin pathway.

Literature review suggests that adherence to immunosuppressive drugs may be lower in recipients of living (related or unrelated) than of deceased donor kidney grafts. In Sudan there no cadaveric donation program is available. Non-adherence was higher among those who received kidney from related donor (62%) than those received from unrelated (43%). Higher non-adherence levels observed in recipients of living donor grafts have previously been attributed to a sense of relative invulnerability resulting from recipients younger age and to the possibility that those receiving grafts from relatives believe that their higher histocompatibility protects them adequately against rejection (Denhaerynck, et al., 2014).
5.4 Beliefs towards immunosuppressants and adherence

Patients’ treatment-related beliefs predict their adherence more strongly than do socio-demographic variables (education, gender, age), clinical variables (type of illness, number of medications), and other beliefs e.g., illness perceptions (Phillips, et al., 2014).

Necessity-Concern framework (NCF) is a useful tool for beliefs measurement and it holds great promise for interventions that aim to improve medication adherence. Researchers have either constructed a difference score (necessity beliefs minus concerns) or artificially categorized patients into attitude groups, which then function as the predictor on a single dimension (Phillips, et al., 2014).

Most kidney transplant participants taking part in this study appeared well informed about their medication and realized how important it was for their wellbeing. They were aware that they must take the drugs, although they knew that the drugs conferred side effects.

All four attitudinal groups that defined using the BMQ Specific necessity and concerns constructs differed with respect to patients adherence about immunosuppressants. Adherence mean score was highest in the accepting group and the ambivalent group, while they were lowest for the indifferent group and the skeptical group. There was significant difference in adherence between Indifferent versus Ambivalent or Accepting groups, but there was insignificant difference in adherence between Accepting and Ambivalent groups. Similar findings were obtained in the study of beliefs about inhaled corticosteroids by Horne, et al., (2008).

The associations found in this study agreed with studies done by Jung, et al., (2010), Lennelling and Forsberg, (2012), Butler, et al., (2004) and Burger, et al., (2015) and indicated that there was a relationship between beliefs and ISD medication adherence. To improve medication intake behavior through targeted interventions, it is important to identify patients who have negative beliefs about their medication. It may however be rather difficult for clinicians to identify these beliefs, particularly if they are not trained in the detection of such beliefs.

Although the majority of patients in this study reported high necessity of taking medication but still nonadherence was very high may be due to definition and assessment of adherence or contributed to other factors that influence adherence.
Chapter Six
Conclusion & Recommendation
6.1 Conclusion:

- GFR declines usually beginning after 30–40 years of age, the rate of decline may accelerate after age 50–60 years.
- Male exhibit a more rapid age-related decline in renal function than female.
- Non adherence to immunosuppressants is very high among Sudanese transplanted population.
- Main reason for non adherence was the forgetfulness.
- Patient age, time post transplantation, serum creatinine concentration, type of donor and beliefs to immunosuppressants were associated with adherence.
6.2 Recommendations:

- Studies with multiple, valid, and reliable measures of adherence that involve using larger samples are needed.
- Because patients have different barriers to medication adherence, it is important to implement an intervention that is tailored to their risk factors in order to improve their adherence rate.
- Counseling sessions by healthcare professionals, continuing patient education about the disease and upgrading patients' socioeconomic levels is recommended.
- Strategies should be developed that can support patients in establishing medication routines and dealing with likely disruptions, along with technology-assisted devices and the simplification of drug regimens and reductions in drug dosage.
- We also recommend the use of pillboxes, keeping a diary and being reminded to take medicine by setting an alarm or planning it to coincide with regular activities like brushing teeth or eating meals.
- An alternative study design should be a prospective cohort study, in which transplant recipients are followed over time. A cohort study would permit correlation of medication adherence with subsequent transplant outcomes, such as rejection or renal function.
References:


Appendix:

Number: …………………………………………………………………………………

1- Age:
   18-28 □  29-39 □  40-50 □  51-61 □  >61 □

2- Sex : Mal□  Feb□

3- Level of education : Low□  Middle □  High □
   None □

4- Time post transplantation  …………

5- Type of donor □
   Deceased donor □  living related □  living unrelated □

6- Lab value
   SCR……………………
   normal level □  above normal level □

7- Last level of immunosuppressants in the blood
   Cyclosporine:-
   out of therapeutic □  therapeutic range □  unknown □

   Tacrolimus :-
   out of therapeutic □  therapeutic range □  unknown □
8- Necessity scale items:

(a) My health at present depend on my medication:
   (i) Strongly disagree ☐ (ii) disagree ☐ (iii) uncertain ☐
   (iv) agree ☐ (v) strongly agree ☐

(b) My medication protect me from getting worse:
   (i) Strongly disagree ☐ (ii) disagree ☐ (iii) uncertain ☐
   (iv) agree ☐ (v) strongly agree ☐

(c) My life would be impossible without my medicines:
   (i) Strongly disagree ☐ (ii) disagree ☐ (iii) uncertain ☐
   (iv) agree ☐ (v) strongly agree ☐

(d) Without my medicines I would become very ill:
   (i) Strongly disagree ☐ (ii) disagree ☐ (iii) uncertain ☐
   (iv) agree ☐ (v) strongly agree ☐

(e) My health in the future will depend on my medicines:
   (i) Strongly disagree ☐ (ii) disagree ☐ (iii) uncertain ☐
   (iv) agree ☐ (v) strongly agree ☐

9- Concerns scale items:

(a) I sometimes worry about becoming too dependent on my medications:
   (i) Strongly disagree ☐ (ii) disagree ☐ (iii) uncertain ☐
   (iv) agree ☐ (v) strongly agree ☐

(b) I sometimes worry about side effects of my medication:
(c) My medicines are a mystery to me:

(i) Strongly disagree □ (ii) disagree □ (iii) uncertain □
(iv) agree □ (v) strongly agree □

(d) My medicines disrupt my life:

(i) Strongly disagree □ (ii) disagree □ (iii) uncertain □
(iv) agree □ (v) strongly agree □

(e) I sometimes worry about the long-term effects of my medicines

(i) Strongly disagree □ (ii) disagree □ (iii) uncertain □
(iv) agree □ (v) strongly agree □

10- Self-reported adherence as measured by ITAS scale:

In the last 3 months, how often did you forget to take your immunosuppressant medication?

none of time □ some times □ often □
very frequent □

In the last 3 months, how often were you careless about taking your immunosuppressant medication?

none of time □ some times □ often □
very frequent □

In the last 3 months, how often did you stop taking your immunosuppressant medication because you felt worse?
In the last 3 months, how often did you miss taking your immunosuppressant medication for any reason?

- none of time
- some times
- often
- very frequent