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The effect of steroids on the development of metabolic syndrome in kidney transplant patients: systematic review

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1. SUMMARY

Author: Rotem Liran.

Title: The effect of steroids on the development of metabolic syndrome in kidney transplant patients.

Introduction: Steroid-sparing regimens have been attempted in recent years among kidney transplant recipients to avoid morbidity from long-term steroid therapy. Different protocols to withdraw steroids after transplantation and their possible benefits vs harms are subject to systematic review. A cluster of adverse effects such as hypertension, obesity, dyslipidemia and diabetes are found to be associated with the use of steroids and this cluster used to define a term "Metabolic syndrome".

Aim: To investigate the effect of steroids on the development of metabolic syndrome in kidney transplant patients

Objectives:

1. To evaluate if early steroids withdrawal prevent development of metabolic syndrome in kidney transplant patients.
2. To evaluate effect of steroids on the development of new onset diabetes after kidney transplantation.
3. To investigate steroid effect on obesity after kidney transplantation.
4. To investigate steroid effect on worsening of hypertension after kidney transplantation

Methodology: A systematic review was conducted through most popular electronic database search using key words as, "kidney" or "renal transplantation", "steroids withdrawal", "obesity", "metabolic syndrome", "hypertension" and "diabetes". A selection of 19 most relevant articles were included, published in the last 15 years, English language and human trials.

Results: This study reviewed and evaluated correlation between steroid use and the appearance of comorbidities which are associated with the term MS. This study showed strong correlation between development of NODAT, use of antihypertensive agents to control HTN, obesity and dyslipidemia – the diagnostic criteria of MS, with steroid usage as compared to withdrawal.

Conclusions: We found association of metabolic syndrome with steroid use, but we could not conclude a specific withdrawal timing to prevent the development in renal transplant patients. This review showed a direct correlation between the use of steroids and the development of insulin resistance and weight gain. Blood pressure was not different the amount of antihypertensive agents was higher in the steroid group as compared to steroid withdrawal in kidney transplant patients.

Recommendations: We recommend a steroid sparing therapy as a protocol in selected patients if risk for development of metabolic syndrome weigh out a risk of rejection. Higher attention should be made in early identification of metabolic syndrome especially in paediatric renal transplant patients in order to prevent this complication.
2. ACKNOWLEDGMENTS

I would like to thank:
Dr. Ruta Vaiciuniene for all her guidance.
Dr. Revital Nassimov and Dr. Luis Manuel Vegas Isasi for valuable recommendations about the research methodology and structure.
3. CONFLICTS OF INTEREST

The author reports no conflicts of interest.
4. CLEARANCE ISSUED BY THE ETHICS COMMITTEE

No clearance issued by the Ethics Committee are needed in this study
5. ABBREVIATIONS

1. Corticosteroids (CS)
2. Hypertension (HTN)
3. New onset diabetes after transplantation (NODAT)
4. Mycophenolate Mofetil (MMF)
5. Calcineurin inhibitors (CNI)
6. Cyclosporine (CsA)
7. Tacrolimus (Tac)
8. High density lipoprotein (HDL)
9. Triglycerides (TG)
10. Metabolic syndrome (MS)
11. Type 2 diabetes (DM2)
12. Impaired fasting glucose (IFG)
13. Impaired glucose tolerance (IGT)
14. Blood pressure (BP)
15. Systolic blood pressure (SBP)
16. Diastolic blood pressure (DBP)
17. Body mass index (BMI)
18. Randomized controlled trials (RCT)
19. Steroid free (SF)
20. Early steroid withdrawal (ESW)
21. Late steroid withdrawal (LSW)
22. End stage renal disease (ESRD)
23. Oral glucose tolerance test (OGTT).
24. Dose twice daily (BD)
25. Dose once daily (QD)
6. TERMS

**Hyperinsulinemic-euglycemic clamp technique**- The plasma insulin concentration is acutely raised and maintained at 100 μU/ml by a continuous infusion. At the same time, plasma glucose concentration is held constant at basal levels and when the steady-state is achieved, the glucose infusion rate equals glucose uptake by all the tissues in the body. Therefore, it is able to measure of tissue insulin sensitivity.

**Oral glucose tolerance testing**- a method which can help to diagnose instances of diabetes mellitus or insulin resistance by a glucose drink and blood glucose level measurements before and at intervals after the sugary drink is taken.

**Lipid profile**- a collection of lipids, evaluated for screening proposes by blood test in order to detect abnormalities in their values including: cholesterol, high density lipoprotein, low density lipoprotein and triglycerides.
7. INTRODUCTION

Transplantation is the most effective method by which organ function is restored in certain disease state. Corticosteroids (CS) have been cornerstone of immunosuppressant regimens since the earliest days of kidneys transplantation [1] [2] [3]. Despite the prevalence in use of steroids as part of treatment regimens, it also associated with numerous adverse effects including hypertension (HTN), hyperlipidaemia, new onset diabetes after transplantation (NODAT) and weight gain, among others [4] [5].

Triple immunotherapy had developed as an attempt to reduce the extent of steroid exposure over the course of the transplanted allograft. Steroids are used for both induction and maintenance immunosuppression together with anti-proliferative agents (azathioprine or mycophenolate mofetil (MMF)) and calcineurin inhibitors (CNI) (cyclosporine (CsA) or tacrolimus (Tac)) [6]. The removal of steroids, due to the side effects, from immunosuppressive protocols has not been easy task. There has been increased interest in protocols utilizing steroids minimization\ withdrawal or complete cessation, but a potential problem of eliminating CS from an immunosuppressant regimen is an increase for acute rejection [7]. As mentioned above, the metabolic factors that are associated with the use of steroids are common in kidney transplant recipients [8]. These combinations obesity, dyslipidaemia (low high-density lipoprotein (HDL) and/or elevated triglycerides (TG)), elevated blood pressure, and alterations in glucose metabolism are associated with a condition known metabolic syndrome (MS) [9] [10].

MS had become highly prevalent in developed nations. Because of morbidity and mortality associated with MS, identifying the root cause of MS had become the focus of many researches [11]. Due to high prevalence and the present data regarding the pathogenesis of steroids use, it is essential to examine the correlation between the use of steroids and the appearance of these comorbidities in kidney transplanted patients. Many studies have shown the appearance of these metabolic factors after transplantation  [12] [13] [14], while others used different immunosuppressant regimens in transplanted patients and compared between reducing dose, maintenance dose or complete elimination of steroids from the therapy [15] [16] [17] [18].

Despite extensive studies on side effects which appear after the use of steroids, there is a continue usage of them in immunotherapy regimes in kidney transplanted patients.

The aim of this review is to investigate the effect of steroids on the development of MS in kidney transplant patients.
8. AIM AND OBJECTIVES

Aim of thesis: To investigate the effect of steroids on the development of metabolic syndrome in kidney transplant patients.

Objectives:

1. To evaluate if early steroids withdrawal prevent development of metabolic syndrome in kidney transplant patients.
2. To evaluate effect of steroid on the development of new onset diabetes after kidney transplantation.
3. To investigate steroid effect on obesity after kidney transplantation.
4. To investigate steroid effect on worsening of hypertension after kidney transplantation.
9. RESEARCH METHODOLOGY AND METHODS

The definition of MS is controversy, with several attempts to specify its components. MS was defined in this review using WHO Clinical Criteria:

1. Insulin resistance, identified by 1 of the following:
   - Type 2 diabetes (DM2)
   - Impaired fasting glucose (IFG)
   - Impaired glucose tolerance (IGT)
   - or for those with normal fasting glucose levels (110 mg/dL), glucose uptake below the lowest quartile for background population under investigation under hyperinsulinemic, euglycemic conditions.

2. Plus any 2 of the following:
   - Antihypertensive medication and/or high blood pressure (BP) (≥140 mm Hg systolic BP (SBP) or ≥90 mm Hg diastolic BP (DBP))
   - Plasma TG ≥150 mg/dL (≥1.7 mmol/L)
   - HDL cholesterol 35 mg/dL (0.9 mmol/L) in men or 39 mg/dL (1.0 mmol/L) in women
   - Body mass index (BMI) ≥30 kg/m² and/or waist:hip ratio ≥0.9 in men, ≥0.85 in women
   - Urinary albumin excretion rate ≥20 g/min or albumin:creatinine ratio ≥30 mg/g [10].

Due to the close similarity in the criteria, we included as well, studies that defined MS by using an adapted version of the National Cholesterol Education Expert Panel (Adult Treatment Panel III [ATP III]) definition. In the present of pediatric population, MS criterion was defined as the presence of any three of five criteria:

- BMI >97th percentile
- HTN (SBP/DBP > 95th per centile or on medications)
- TG > 95thpercentile
- HDL cholesterol < 5th percentile
- Fasting glucose > 100 mg/dL.

Search strategy:

This systematic review was conducted using the most popular databases: Nature, BMC, PubMed, BMJ, OXFORD academic and Wiley library. By following the PRISMA (preferred reporting items for systematic reviews and meta-analysis) statement, we identify studies concerning CS use and the appearance of comorbidities in renal transplant patients. Date of publication was focused until 15
years. In the search engine we search for specific key words as, "kidney transplantation" or "renal transplantation", "steroids withdrawal", "obesity", "MS", "HTN" and "diabetes" according to our objectives.

**Study selection:**
Relevance to the research was predefined by inclusion criteria:

1. Patients after kidney transplantation (adults and children)
2. Intervention includes immunosuppressive therapy with steroid use (in different dosage and regimens).
3. Evaluation of outcomes (MS, NODAT, obesity, HTN) post withdrawal or elimination in comparison to regular therapy.
4. Study type: randomized controlled trials (RCT), controlled clinical trials (non-randomized-trials), and cohort studies.
5. Publication language: English; last 15 years publications and human trails

Exclusion criteria:

1. Non-human trails
2. Immunotherapy without CS usage
3. Studies that did not included relevant outcomes.

**Data collection:**
A total of 633 studies were identified based on the key words search, of which 358 were excluded due to publication time of more than 15 years and non-human trails. Another reduction of n=224 studies due to title review and duplications, left us with n=51 studies to be evaluated by abstract and full text review. Finally, n=19 studies were conducted according to inclusion and exclusion criteria. These were prospective randomized, prospective cohort, and retrospective studies (Figure. 1).
Data analysis:

Data was abstracted by one investigator and from each report we determined year of publication, number of total participants plus the number of participants in each regimen protocol, age, type of therapy regimens that were compared in the studies and duration of the study (Table 1).
Table 1. Characteristics of the Enrolled Studies

1. Non randomized-

<table>
<thead>
<tr>
<th>Nr.</th>
<th>Author</th>
<th>Year</th>
<th>Participants</th>
<th>Age</th>
<th>Therapy</th>
<th>Duration</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Van den Ham</td>
<td>2003</td>
<td>123</td>
<td>≥18</td>
<td>57</td>
<td>66</td>
<td>5 years CsA vs CsA+CS</td>
</tr>
<tr>
<td>2</td>
<td>L.Li</td>
<td>2009</td>
<td>186</td>
<td>0–21</td>
<td>129</td>
<td>57</td>
<td>0.8–8.8 years Dac\Tac\MMF vs CS\Dac\Tac\MMF</td>
</tr>
<tr>
<td>3</td>
<td>Silverstein</td>
<td>2005</td>
<td>22</td>
<td>1–20 yr.</td>
<td>11</td>
<td>11</td>
<td>1 year post transplanted Dac\Tac\MMF Retrospective</td>
</tr>
<tr>
<td>4</td>
<td>Bhakta</td>
<td>2008</td>
<td>49</td>
<td>1–20 yr.</td>
<td>19</td>
<td>30</td>
<td>1 year post transplanted Tac\MMF\Dac vs CS\Tac\MMF\Dac</td>
</tr>
<tr>
<td>5</td>
<td>Kumar</td>
<td>2006</td>
<td>300</td>
<td>≥20 yr.</td>
<td>150</td>
<td>150</td>
<td>3 YEARS Tac\CsA\MMF or SRL vs CS\Tac\CsA\MMF or SRL Randomization-cancelled.</td>
</tr>
<tr>
<td>6</td>
<td>Haririan</td>
<td>2006</td>
<td>73</td>
<td>30–60 yr.</td>
<td>40</td>
<td>33</td>
<td>1 year Retrospective</td>
</tr>
<tr>
<td>7</td>
<td>Maduram</td>
<td>2010</td>
<td>58</td>
<td>5–18 yr.</td>
<td>33</td>
<td>25</td>
<td>1 year Tac or CsA\MMF or azathioprine or SRL vs CS\Tac or CsA\MMF or azathioprine</td>
</tr>
<tr>
<td>8</td>
<td>Phalen</td>
<td>2011</td>
<td>241</td>
<td>≥18 yr.</td>
<td>53</td>
<td>69 (&lt;5 mg) 119 (&gt;5 mg)</td>
<td>1 year Tac\MMF\CS</td>
</tr>
<tr>
<td>9</td>
<td>Lemieux</td>
<td>2003</td>
<td>26</td>
<td>≥18 yr.</td>
<td>16 ± 2.9</td>
<td>≥10 mg</td>
<td>CS\CsA</td>
</tr>
</tbody>
</table>
10. Tillman

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Participants</th>
<th>Age</th>
<th>Therapy</th>
<th>Duration</th>
<th>Therapy</th>
<th>Cohort study</th>
<th>Prospective Pilot</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tillman</td>
<td>2012</td>
<td>187</td>
<td>≥18 yr</td>
<td>Decreasing dose CS Tac or CsA or and MMF</td>
<td>≤7.5</td>
<td>Prospective Pilot</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

11. Cole

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Participants</th>
<th>Age</th>
<th>Therapy</th>
<th>Duration</th>
<th>Therapy</th>
<th>Cohort study</th>
<th>Prospective Pilot</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cole</td>
<td>2013</td>
<td>49</td>
<td>≥18 yr</td>
<td>Decreasing dose CS Tac or CsA or MMF</td>
<td>6 months</td>
<td>Prospective Pilot</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

12. Porrini

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Participants</th>
<th>Age</th>
<th>Therapy</th>
<th>Duration</th>
<th>Therapy</th>
<th>Cohort study</th>
<th>Prospective Pilot</th>
</tr>
</thead>
<tbody>
<tr>
<td>Porrini</td>
<td>2006</td>
<td>230</td>
<td>30-60 yr</td>
<td>Decreasing dose CS Tac or CsA or MMF</td>
<td>1 year-2.5 years post transplantation</td>
<td>Cohort study</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. Randomized studies-

<table>
<thead>
<tr>
<th>Nr.</th>
<th>Author</th>
<th>Year</th>
<th>Participants</th>
<th>Age</th>
<th>Therapy</th>
<th>Duration</th>
<th>Therapy</th>
<th>Cohort study</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rostaing</td>
<td>2005</td>
<td>551</td>
<td>18 – 65</td>
<td>SF/CS</td>
<td>6 months</td>
<td>Tac/MMF/CS vs Dac/Tac/MMF</td>
<td>Randomization</td>
</tr>
<tr>
<td>2</td>
<td>Fijter</td>
<td>2018</td>
<td>297</td>
<td>18 and 80 yr</td>
<td>SF/CS</td>
<td>6 months</td>
<td>Tac/MMF vs Tac/MMF/CS</td>
<td>Randomization</td>
</tr>
<tr>
<td>3</td>
<td>Gheith</td>
<td>2010</td>
<td>100</td>
<td>22-56 yr</td>
<td>SF/CS</td>
<td>1 year</td>
<td>MMF/Tac vs MMF/Tac/CS</td>
<td>Randomization</td>
</tr>
<tr>
<td>4</td>
<td>Mervilla</td>
<td>2017</td>
<td>1081</td>
<td>≥18</td>
<td>SF/ESW/CS</td>
<td>6 months</td>
<td>Tac\basiliximab/MMF\CS vs Tac\basiliximab/MMF</td>
<td>Randomization</td>
</tr>
<tr>
<td>5</td>
<td>Vincenti</td>
<td>2008</td>
<td>337</td>
<td>18-75 yr</td>
<td>SF/ESW/CS</td>
<td>1 year</td>
<td>CsA\EC-MPS\basiliximab vs CS\CsA\EC-MPS\basiliximab</td>
<td>Randomization</td>
</tr>
</tbody>
</table>

LSW CS
<table>
<thead>
<tr>
<th></th>
<th></th>
<th>2010</th>
<th>42</th>
<th>6-14 yr</th>
<th>23</th>
<th>19</th>
<th>2 years</th>
<th>CsA/MMF vs CsA/MMF</th>
<th>Randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Britta</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>7</td>
<td>Yates</td>
<td>2014</td>
<td>22</td>
<td>18-75 yr</td>
<td>11</td>
<td>11</td>
<td></td>
<td>Tac/MMF/CS</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
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</tbody>
</table>

SF- steroid free; CS- corticosteroids; ESW- early steroid withdrawal; LSW- late steroid withdrawal. Tac- tacrolimus; MMF- Mycophenolate mofetil; Dac- daclizumab; CsA-cyclosporine; EC-MPS- Enteric-Coated Mycophenolate Sodium.
10. RESULTS

Characteristics of the included studies:

In this section we reviewed the results of randomized studies (n=7), which include 2481 patients (adults n= 1400, n=1081 pediatric) undergoing renal transplantation. Out of them n= 935 patients received steroid free (SF) therapy, n= 304 patients were early steroid withdrawal (ESW) and n= 23 late steroid withdrawal (LSW), compared to n= 1219 patients on CS therapy; and non-randomized studies (n=12), which included n=1544 patients (adults n= 1229, n=315 pediatric) undergoing renal transplantation. Out of them n=269 patients received SF therapy, n= 292 patients were ESW and n=26 LSW, compared to n=957 patients on CS therapy. All these reviewed studies were included according to inclusion and exclusion criteria, mention in the methodology section.

10.1 New onset diabetes after transplantation

As we mention previously, insulin resistance is an obligatory feature in the diagnostic criteria of MS; it is compose of diagnosis of DM2, IFG or IGT. Comparison of prevalence of insulin resistance in CS group vs ESW group in randomized clinical studies is shown in table 2.

Randomized studies-

Table 2. The prevalence of insulin resistance in study groups in randomized studies

<table>
<thead>
<tr>
<th></th>
<th>ESW</th>
<th>CS</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fijter et al</td>
<td>24.7%</td>
<td>34.3%</td>
<td>0.310</td>
</tr>
<tr>
<td>Gheith et al</td>
<td>4%</td>
<td>16%</td>
<td>0.037</td>
</tr>
<tr>
<td>Rostaing et al</td>
<td>0.4%</td>
<td>5.4%</td>
<td>0.003</td>
</tr>
<tr>
<td>Merville et al</td>
<td></td>
<td></td>
<td>0.579</td>
</tr>
</tbody>
</table>

We can see that statistical significance was found in a randomized, multicenter study conducted by Rostaing et al [19]. A total of 551 renal transplant patients were evaluated for 6 months. The control group included 278 patients treated with CS, while the experimental group (n=260) were treated with SF regimen; the therapy was initiated after randomization. NODAT was found in higher number of participants in CS group; additionally, adverse event of hyperglycemia was 15.8% in
control group (n=44) and 13.1% in experimental group (n=34). The study suggests that in the absence of steroids, there is reduced diabetogenic potential of Tac-base therapy and that SF regimen present advantage in terms of a lower incidence of NODAT. In another randomized study, Gheith et al [20] aimed to assess the cost- benefit of ESW regimen. A total of 100 patients were randomized and divided into control CS group (n=50) and experimental ESW group (n=50). Patients were evaluated for fasting and postprandial venous plasma glucose level. The median follow-up was 12 months and a p value <0.05 considered statistically significant. The results showed significantly higher percentage of cases with NODAT in CS group, supporting that steroid avoidance is feasible, safe and had less associated with NODAT. In contrast, other studies did not find differences in NODAT in different CS regimens. For instance, Fijter et al [21] studied 297 kidneys transplant recipients during 6 months. Study results showed, higher percentage of NODAT in CS group, but since the baseline characteristic was different in regard to DM2 prevalence (24.2% vs 14.4) the increase was not significant. Another multicenter prospectively randomized study Mervilla et al [16] analyzed n=1081 patients for 6 months. There were no significant differences between arms in the presence of NODAT at week 24.

**Non randomized studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>SF</th>
<th>CS</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li et al</td>
<td>0.80%</td>
<td>9%</td>
<td>p= 0.0089</td>
</tr>
<tr>
<td>ESW</td>
<td></td>
<td>CS</td>
<td></td>
</tr>
<tr>
<td>Kumar et al</td>
<td>4%</td>
<td>21%</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>Harrian et al</td>
<td>13%</td>
<td>22%</td>
<td>p = 0.4</td>
</tr>
<tr>
<td>Cole et al</td>
<td>12%</td>
<td>33%</td>
<td>N.S*</td>
</tr>
<tr>
<td>Phalen et al</td>
<td>0%</td>
<td>8%</td>
<td>p = 0.088</td>
</tr>
</tbody>
</table>

* N.S -not specified

Table 3 summarizes the non-randomized studies showing the appearance of insulin resistance in correlation with different type of CS therapy.

L.Li et al [22] present single center study, with n= 129 pediatric renal transplant patients on SF protocol in comparison to cohort group of n= 57 patients treated with CS regimen. They found low rates of NODAT in SF group, demonstrated the safety and reduction of steroid side effects by using SF regimen for kidney transplantation in pediatric recipients. Furthermore, three other similar studies were done by Cole et al [15], Kumar et al [23] and Haririan et al [24] and examined the impact of ESW with
association to NODAT. The studies have found that ESW caused significantly lower incidence of NODAT in comparison to CS group.

10.2 Hypertension

HTN is one of diagnostic criteria for MS; it was diagnosed when blood pressure was ≥140 mm Hg systolic or ≥90 mm Hg diastolic and/or the use of antihypertensive medications.

Randomized studies-

Table 4. The percentage of patients using antihypertensive agents- randomized studies

<table>
<thead>
<tr>
<th></th>
<th>SF</th>
<th>ESW</th>
<th>CS</th>
<th>LSW</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vinceti et al</td>
<td>80%</td>
<td>81%</td>
<td>88%</td>
<td>-</td>
<td>N.S*</td>
</tr>
<tr>
<td>Britta et al</td>
<td>-</td>
<td>-</td>
<td>93%</td>
<td>50%</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>Gheith et al</td>
<td>-</td>
<td>4%</td>
<td>44%</td>
<td>-</td>
<td>P=0.0009</td>
</tr>
<tr>
<td>Rostaing et al</td>
<td>39%</td>
<td>-</td>
<td>44%</td>
<td>-</td>
<td>N.S*</td>
</tr>
</tbody>
</table>

*N.S -not specified

Table 4 summarizes the randomized studies showing the usage in antihypertensive agents in HTN patients in correlation with different type of CS therapy.

Vincenti et al [25] compared the benefits of different CS regimens (SF vs. ESW vs. CS therapy) on BP. In this study randomization divided 337 patients into groups in a ratio of 1:1:1. By the end of 12 months, no differences were observed in terms of a use of antihypertensive medications. In contrary, Gheith et al [20] did present differences between the groups; most patients on SF group stopped taking any antihypertensive agent shortly after transplantation (from 24% reduced to 4%), while 75% of hypertensive patients in the CS group increased the amount of agents from 1 pre-transplantation to 3 agents by the end of the study. Furthermore, in multicentre, randomized study Britta et al [26] compared LSW (>1-year post transplant) with ongoing CS in a group of 40 pediatric patients. The patients were randomized and divided to LSW group (n= 23) and CS group (n=17). LSW was associated with significant reduction of HTN over the first year, this effect persisted during the
second year (mean BP reduced in LSW group from 0.78± 0.27 to 0.53± 0.27 SDS); in addition, LSW group required significantly less antihypertensive agents (p<0.05). Rostaing et al [19] present similar results between the groups; 15.1% in CS in comparison to 15.8% in SF appeared with HTN during the study period.

**Non randomized studies**-

Two studies Silverstein et al [27] and Phalen et al [4] showed different results. The first, found that at 6, 9, and 12 month after transplantation, SBP was slightly lower in the SF group, but this did not reach statistical significance at any time point (p=0.14). However, CS group required more medications to lower BP (similar to the results of randomized studies). Similarly, the results of a second study did not reach statistical significance.

**10.3 Obesity**

According to the criteria for MS, obesity is one of diagnostic factors; composing of BMI ≥30 kg/m2 and/or waist:hip ratio ≥0.9 in men, ≥0.85 in women.

**Randomized studies**-

When analyzing obesity, we observed two studies reporting this adverse event. In both studies, results showed BMI drop in all steroid minimization regimens (SF\ESW\LSW groups) in comparison with CS group [25] [26]. Vincenti et al [25] stated a statistically significant BMI decreased in the withdrawal group (p=0.008). Britta et al [26] showed significant BMI dropped by 0.68±0.23 SDS in LSW group, whereas the BMI in patients of the control group rose significantly by 0.26±0.34 SDS.

**Non-randomized studies**-

In retrospective study Van den Ham et al [28] examined patients in the first 5 years post renal transplantation: 66 patients in the control group (CS group) and 57 patients on experimental group (SF). The results of the study showed no differences in the weight gain in both groups during the first year post transplantation. The positive relationship of weight gain and CS use was observed only after first year (from 74.3 to 77.9 kg in CS group (P<0.00) and from 70 to 71.2 kg in SF group (P= 0.08)). A study conducted by Lemieux et al [29] followed 26 renal transplant patients before and after at least 11 months of CS withdrawal. Subjects were first evaluated three to four years after transplantation and re-evaluated for risk factors following CS withdrawal at average of 16 months. The results were compared between males and females. Significant weight loss (-6.04%) and BMI reduction (-
1.72±2.10 kg/m²) was noted in women post CS withdrawal (P =0.05) whereas no changes were observe in men. L.Li et al [22] present single center study, with 129 children post renal transplantation on SF protocol, with mean follow of 5 years. Mean BMI change in 2 years was 1.6 kg/m² in SF vs 3.8 kg/m² in CS group (p = 0.02). Bhakta et al [30] presented similar comparison between CS and SF groups in 49 paediatric renal transplanted recipients. The results of weight and BMI were compared and showed significantly difference in both delta Z score (weight P=0.03, BMI P=0.009). The study conclude it results and recommend nutritional and exercise support is needed in any paediatric renal transplantation with CS therapy due to the weight gain and BMI changes that were observe in this group. Two studies, conducted by Silverstein et al [27] and Phalen et al [4] found similar BMI levels between the groups (p =0.08 and p = 0.66 respectively).

10.4 Dyslipidemia

According to MS criteria, dyslipidemia could be used as diagnostic feature; composed of plasma TG ≥150 mg/dL (≥1.7 mmol/L) or and HDL cholesterol 35 mg/dL (0.9 mmol/L) in men or 39 mg/dL (1.0 mmol/L) in women.

**Randomized studies-**

<table>
<thead>
<tr>
<th></th>
<th>HDL mg/dL</th>
<th>TG mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gheith et al</td>
<td>ESW</td>
<td>59.7±11.1</td>
</tr>
<tr>
<td></td>
<td>CS</td>
<td>44.3±13.1</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>0.04</td>
</tr>
<tr>
<td>Britta et al</td>
<td>LSW</td>
<td>49±2.7</td>
</tr>
<tr>
<td></td>
<td>CS</td>
<td>49.6±3.6</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>N.S</td>
</tr>
</tbody>
</table>

Two studies present mean prevalence of dyslipidemia in their results; both of these studies showed statistically significant difference in the changes of both TG and HDL. In the first study, Gheith et al [20] showed significant elevation of mean TG and significant reduction of HDL among patients on CS therapy after one year as compared to ESW (86.7±15.3 vs 119.6±27.2, 38.2±5.1 vs 44.3±13.1 respectively). Furthermore, in study of Britta et al [26], HDL cholesterol concentration remained unchanged in both groups, while difference of TG concentration did reach statistical significance (Table 5).
Non randomized studies-

The group of non-randomized studies did not present such definitive results. L.Li et al [22] present reduction in TG in 26% vs 50% in SF group as compared to CS group in a mean follow of 5 years. In contrary, Lemieux et al [29] compared between genders with LSW. The results showed reduction in HDL cholesterol level in both genders (-14% women vs -22% in men, P < 0.005) while no TG changes were seen before and after withdrawal (2.08 ±0.94 vs 2.13± 0.95). Silverstein et al [27] showed higher measurements of lipid profile in the CS group, but results did not reached statistical significance (p=0.8).

10.5 Metabolic syndrome

As we mention previously, the diagnostic criteria of MS composed out of combination of different comorbidities. Only non-randomized studies tested outcomes of different steroid regimens on development of MS. Porrini et al [31] compared CS tapering rather than CS withdrawal and aimed to evaluate transplant recipient without diabetes for the prevalence of MS and the evolution to diabetes. 230 patients were included in the study, of them 52 patients (22.6%) presented with MS at baseline and 178 patients (77.3%) did not. At the end of the study (mean of 4 years) MS proportion was increased to 37.7% (reaching statistical significant P < 0.001). Nineteen patients were diagnosed with NODAT at baseline; NODAT beyond 1 year after transplantation was common in the MS group, whereas a rare event in the non–MS group (P < 0.001). Similar significance appeared in other components associated with this syndrome: BMI (P<0.001) and TG (P =0.005). In a study with pediatric recipients, Maduram et al [32] aimed to assess the prevalence of MS between ESW vs CS group. Each group was evaluated separately, presenting MS prevalence of 68% (n=17) in CS group and 15% (n=5) in ESW group (p < 0.00001). Over the entire study, serum glucose was significantly lower in ESW group 96± 15 vs 104 ±15 in CS group. Lipid profile was lower in ESW group. SBP and DSB were not significantly different. However the use of antihypertensive agents was 88% (n=22) on CS group and 70% (n=23) on the ESW group (p = 0.002). The study results suggest that ESW therapy produce better outcomes in regard to the incidence of MS.
11. DISCUSSION

MS became highly prevalent worldwide regardless to transplantation. The definition of MS compose of complex of factors and comorbidities, that is found to be more common in renal transplanted recipients than in other end stage renal disease (ESRD) patients. This systematic review tried to provide a collection of evidence showing the outcomes of CS usage in renal transplantation with correlation to MS criteria.

A major side effect of CS and main criteria in the diagnosis of MS has been the development of DM2 [5]. Our reviewed studies showed almost equal results in both randomized and non-randomized studies. The higher incidences of NODAT in CS group indicate direct correlation between the steroid usage and the appearance of the disease. Supporting finding was also found in prospective study conducted in 2012 for evaluation not NODAT but rather the pre diabetic’s risk factors that appear post kidney transplantation. The patients received same dose of CS during the whole study and pre diabetic state (IFG, IGT) were evaluated by oral glucose tolerance test (OGTT). 30.5% (57 patients) was diagnosed with pre-diabetic (IFG, IGT, IFG+IGT). These results well correlate with the criteria for insulin resistance in MS definition [33]. Another conducted study, Yates et al [17] a randomized study, aim to compare the glycaemic effect of divided CS dose twice daily (BD) versus once daily (QD). The patients (n=22) were continuously glucose monitored for 5 days, during this time mean glucose, peak glucose and hyperglycemia were assessed. The study results showed BD therapy was associated with decrease mean glucose in compare with QD therapy (7.9± 1.7 vs 8.1± 2.3, P < 0.001). The study results show another correlation between dividing dose of CS and glucose changes, regardless to the association that was found between CS and

In addition, another important factor in the development of MS is HTN. The vast majority of the studies did not find any difference in the terms of SBP/DBP [19] [20] 25. However, a difference was found regarding reduction in the use of antihypertensive agents. A good example for this reduction was presented in Gheith et al [20]. The study reported that most patients on SF group stopped taking any agent shortly after transplantation (from 24% reduced to 4%), while 75% of HTN patients in the CS group increased the amount of antihypertensive agents from 1 pre-transplantation to 3 agents by the end of the study. Interesting point came up in one year pediatric study, published by Silversein et al [27], which explained the BP similarity between the CS regimens. Authors state that although SBP was similar in both SF and CS groups, it may be achieved as a result of higher amount of antihypertensive agents to control BP in the CS group. Thus, we can assume that CS use did cause HTN worsening, but is not expressed due to higher number of antihypertensive agents.

Besides NODAT and HTN, another important factor to be evaluated is obesity. In 2 randomized studies we observed reduction in BMI after CS withdrawal [25] [26]. Supporting these
results, Van den ham et al [28] studied the changes in body weight after renal transplantation. Although authors didn’t show change in body weight between CS and SF group in the first year post transplantation, they found correlation between cumulative steroid dose and weight gain. After adjusting the characteristics between different steroid use groups (age, baseline BMI, sex, pre-transplant diabetics). Harrian et al [24] also found association between weight gain and steroid use. Additionally, reports in pediatrics population showed same association [22] [27] [33].

The pathogenesis of dyslipidemia in renal transplant patients is poorly defined, it has been reported that immunosuppressive therapy; specifically CS effect, may be one of the causes for abnormal lipid metabolism [5] [8]. Therefore, dyslipidemia is another important factor to be discussed. The reviewed results showed improvement in lipid profile post withdrawal [20] [29]. Correspondingly, similar results appears on other pediatric reports [22] [26]. Thus, we can correlate between the CS usage and the change in lipid metabolism.

The reviewed results has shown association between steroid minimization post renal transplantation (SF\ ESW or LSW) and significant reduction in BMI, a significant reduction in use of antihypertensive agents, improvement in lipid profile and a significant reduction in the prevalence of NODAT in comparison with CS or low dose CS usage. The results of these complex factors, let us to conclude that MS prevalence in renal transplant population correlate with withdrawal of CS. However, we did not find a correlation regarding to withdrawal timing on the appearance of MS, since we found improvement in the parameters in SF in similar fashion as ESW. Despite the increased interest in SF immunosuppressive protocol due to the well-known side effect of CS, there is no possibility to completely evaluate CS effect solely and this is a major limitation of our review. The immunotherapy regimen, given to the recipient, always composed out of combination of medication, each by itself may induce other adverse effect and some may increase the CS adverse effect, while the others will decrease.

Future studies should evaluate the change of CS along with similar immunosuppressive protocol, since many studies changed not only CS regimens but rather one or two other agents. In addition, future trials should inspire to improve methodological quality with double blinding and adequate randomisation, in order to produce more reliable results. Finally, longer follow up of studies outcomes could be useful tool for more specific outcomes of CS elimination.
12. CONCLUSIONS

1. We found association of metabolic syndrome with steroid use, but we could not conclude that early steroid withdrawal solely prevent the development of metabolic syndrome in renal transplant patients.

2. This review showed a direct correlation between the use of steroids and the development of insulin resistance after kidney transplantation.

3. We found association between the corticosteroid withdrawal and weight loss in renal transplant patients.

4. Blood pressure was not different but the amount of antihypertensive agents was higher in the steroid group as compared to steroid withdrawal after kidney transplantation.
13. **RECOMMENDATIONS**

We recommend a steroid sparing therapy as a protocol in selected patients if risk for development of metabolic syndrome weigh out a risk of rejection. Higher attention should be made in early identification of metabolic syndrome especially in paediatric renal transplant patients in order to prevent this complication.
14. REFERENCES


