Case presentation
AKI

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Nephrologist

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Case presentation

- شکایت اصلی:

ضعف عضلانی و استفراغ

- **شرح بیماری فعلی :**

- خانم ۶۴ ساله با سابقه دیابت فشار خون بالا و بیماری ایسکمیک قلب به دلیل تهوع و استفراغ که از ۱۰ روز قبل شروع شده مراجعه کرده وی از احساس سستی و ضعف عضلات شاکی بوده که در سه روز گذشته تشدید شده و خواب الودگی نیز به آن اضافه شده است وی مدعیست که در طی چند روز گذشته دفعات و حجم ادرار کاهش یافته است. از روز قبل از بستری دچار اسهال آبکی شده که سه بار در روز بوده
- در سوابق وی دیابت و فشار خون بالا از ۳۰ سال قبل و بیماری ایسکمیک قلب از ۳ سال قبل گزارش شده

شرح حال دارویی

- Tab Metformin **Sitagliptin** >> BD
- Tab Synoripa 5/500 >> Daily
- Tab Nitrocontin 6.4 >> BD
- Tab ASA 80 >> Daily
- Tab Gliclazid 60 >> Daily
- Tab Valzomix 5/160 >> Daily
- Tab Rosuvastatin 40 >> Daily
- Tab Gabapentin 100 >> Daily
- Tab Osvix 75 >> Daily
- Tab Indapamid 2.5 >> Daily
- Tab Hydrochlorothiazid 25 >> Daily
- Tab Escitalopram 10 >> Daily
- Pen Insulin Lantus 30 unit

معاینه

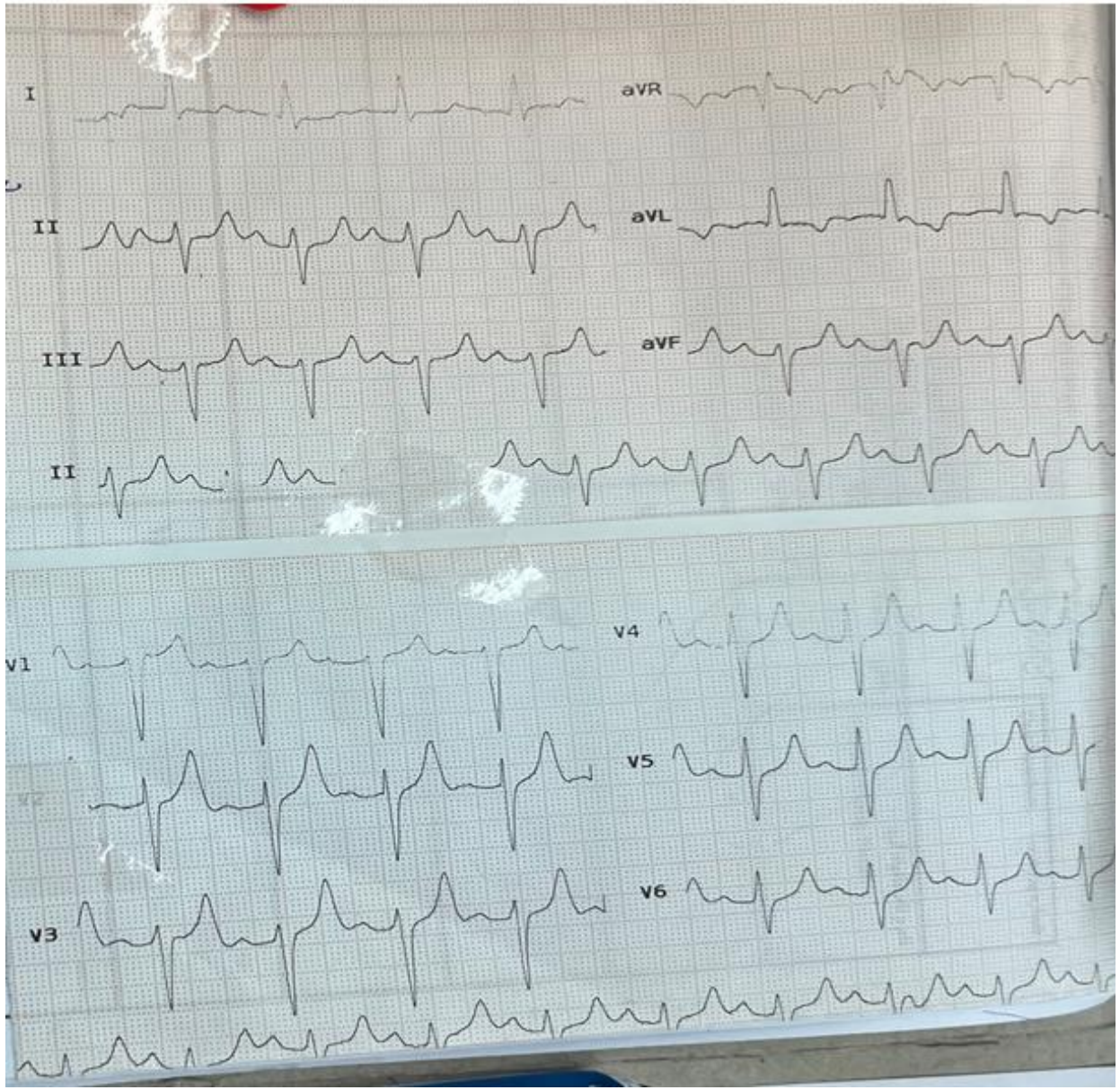
- علایم حیاتی
- T : 37 - RR : 20 /min - PR : 97/mim - BP : 133/67 mmHg - O2 SAT :96%

  H : 156 cm - W : 65 kg
- سر و گردن نکته ای نداشت مردمکها قرینه بود و پاسخ به نور طبیعی بود مخاط دهان و بینی خشک بوده در حالت خوابیده ورید های گردنی دیده نمی شده سمع ریه نرمال بوده در سمع قلب صداهای اول و دوم بخوبی شنیده میشده و صدای اضافه نداشت شکم نرم بوده و حساسیت نداشت صداهای روده ای طبیعی شنیده میشد . نبض های محیطی قرینه بوده و با قدرت و دامنه طبیعی لمس میشده ادم اندام تحتانی ۳ مثبت داشت سایر معاینات نکته قابل توجهی نداشت

آزمایشات

	7/5	7/8	7/10	7/12	7/14	7/16	7/18
P (mg/dl)	7.6	6.09	5.4	5.3	5.62	6.33	6.92
Ca (mg/dl)	8.6	7.97	7.9	8	8.94	9.70	9.80
K (meq/l)	8	5.3	5.1	5.9	5.5	4.8	4.7
Na (meq/l)	131	130	124.9	133.2	141.5	144	139.5
Mg (mg/dl)	2.4	2	1.9	1.81	2.42	2.6	2.51
LDH	1464	1900	1494	1076	968	949	801
CPK (U/L)	22000	12000	5530	2830	**	**	**
Alb (g/dl)	3.3	2.6	2.5	2.6	2.4	2.6	2.8
BUN (mg/dl)	132	131	141	149	145	143	116
Cr (mg/dl)	**9.97**	10.24	10.1	11.1	10.93	10.64	8.74
Hb	11.1	9.5	8.7	8.3	8.5	8.1	7.9
WBC	11.8	6.7	6.9	6.6	6.9	7.6	7.6
PLT	309	263	271	263	287	335	358
Uric acid (mg/dl)	9.7	9	9.3	10.3	9.6	10	7.9

EKG



سونو گرافی

- هر دو کلیه ابعاد طبیعی دارند
- RT KIDNEY :122 CM LT KIDNEY:112CM
- اکوژنیسیته پارانشیم کورتیکال و افتراق کورتیکومیدولاری دو طرف طبیعی است.
- ضخامت پارانشیم در هر دو طرف طبیعی است.
- تصویر سنگ در سیستم پیلوکالیسال وجود ندارد.
- هیدرونفروز در سمت چپ دیده نشد.
- Fullness کلیه راست دیده شد.
- مثانه خالی و واجد بالون سوند فولی است.

Intake & urin Output

1800	7/5	7/6	……	7/15	7/16	7/17	7/18
In take	2460	1080	…….	635	550	1350	1190
Out put	1800	1400	…….	1380	1800	1610	1585

تشخیص اولیه

- بیمار با تشخیص نارسایی حاد کلیه در بیمارستان بستری شده
- با توجه به علایم و نشانه ها هیپرکالمی ، هیپر فسفاتمی ، هیپریوریسمی و افزایش CPK

تشخیص نارسایی حاد کلیه به دلیل رابدومیولیز

اقدامات درمانی اولیه در اورژانس در بدو ورود

- آزمایشات اولیه
- سونوگرافی کلیه و مجاری ادراری
- قرص Indapamide 1.5 <<<hold
- قرص Hydrochlorothiazid20 <<<hold
- با توجه به k>8 آمپول گلوکونات کلسیم شروع شد
- سرم دکستروز ۱۰% ، ۵۰ سی سی در ساعت و دو ویال سدیم بی کربنات
- S/E & S.C
- 10 واحد انسولین رگولار

اقدامات در مانی

- قرص Rosovastatine40 <<< Hold
- قرص Atorvastatin40
- قرص Citalopram <<<hold
- با توجه به هایپوناترمی محدودیت آب
- بی کربنات سدیم وریدی
- شروع انسولین
- قطع داروهای خوراکی کنترل قند
- و درمان حمایتی

سیر بیماری

- بیمار روزانه از نظر وضعیت بالینی و نیاز به دیالیز اورژانس بررسی میشده
  بررسی ها شامل انجام ازمایشات CBC , LDH , P, Ca , cpk, uric acid, K, Na
- کنترل حجم مایعات مصرفی و دفعی
- معاینات روزانه
- نهایتا در روز ۱۲ بستری و پس از ۳ روز متوالی کاهش کراتینین و بهبود وضعیت کلینیکی بیمار مرخص شد
- در ازمایشات روز ۲۵ مهر ماه (۷ روز بعد از ترخیص)

FBS = 161 mg/dl UREA = 149 mg/dl Cr = 5.01 mg/dl

Ca=9.7 mg/dl P=4.8 mg/dl Na= 143 meq/L K=4.1 meq/L

Petejova and Martinek *Critical Care* 2014, 18:224
http://ccforum.com/content/18/3/224

CRITICAL CARE

REVIEW

Acute kidney injury due to rhabdomyolysis and renal replacement therapy: a critical review

Nadezda Petejova* and Arnost Martinek

- Rhabdomyolysis (RM) is a clinical syndrome characterized:
  - Injury to skeletal muscle fibers
    - Release of their contents into the circulation.
      - Myoglobin
      - Creatine phosphokinase (CK)
      - Lactate dehydrogenase

The history of Rhabdomyolysis

- Back to the Second World War in 1941
- Bombing of many cities in the United Kingdom
  - Crush injuries led to typical symptoms of Rhabdomyolysis
- Today (know the causes of RM)

Acquired	Hereditary
Extreme physical activity	Metabolic myopathies caused by disorders of:
Influence of extreme temperatures	Fatty acid oxidation
Metabolic disorders of water and salts	Mitochondrial metabolism
Trauma and crush syndrome	Glycolysis/glycogenolysis
Vascular ischemia	Purine nucleotide cycle
Influence of drugs	Pentose phosphate pathway
Infections, sepsis	
Toxins	
Malignant hyperthermia	
Endocrine disorders	
Electrical current	

Clinical symptoms

- Myalgia
- Weakness
- Swelling
- Usually associated with myoglobinuria
- AKI due to rhabdomyolysis occurs in 13 to 50% of all cases
  - Typical metabolic alterations
    - Hyperkalemia
    - Metabolic acidosis
    - Hypocalcemia
    - Hypercalcemia
    - Hyperuricemia
    - Hyponatremia
    - Hyperphosphatemia

Etiology of rhabdomyolysis and myopathies

Acquired	Hereditary
Extreme physical activity	Metabolic myopathies caused by disorders of:
Influence of extreme temperatures	Fatty acid oxidation
Metabolic disorders of water and salts	Mitochondrial metabolism
Trauma and crush syndrome	Glycolysis/glycogenolysis
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Pathophysiology

- The most serious consequence of RM is ATP depletion, resulting in membrane cell pump dysfunction
- High concentration of Ca persists in the sarcoplasm activates cytolytic Enzymes
  - Hydroxylases
  - Proteases
  - Nucleases and many others
- The result of cell impairment is release substances into the blood circulation
  - Potassium
  - Phosphates
  - Myoglobin
  - CK
  - Lactate dehydrogenase
  - Aldolase

Typical clinical presentation of RM

Diagnosis of rhabdomyolysis and following acute kidney injury

Clinical presentation
Muscular weakness, myalgia, swelling, tenderness, stiffness
Fever, feelings of nausea, vomiting, tachycardia
Oligoanuria or anuria in connection with renal damage or in the presence of volume depletion
Signs of the underlying disease
Laboratory findings
Serum: creatinine, urea nitrogen, creatine phosphokinase, myoglobin, ions (potassium, phosphorus, calcium), lactate dehydrogenase, transaminases, acid–base balance
Urine: myoglobin or positive dipstick test without any erythrocytes

Conservative measures in rhabdomyolysis to prevent acute kidney injury

- The first step is usually treatment of underlying disease
- Massive hydration
- Conservative management

Conservative measures (Diuretic agent – mannitol)

Bragadottir *et al. Critical Care* 2012, **16**:R159
http://ccforum.com/content/16/4/R159

CRITICAL CARE 2012

RESEARCH Open Access

Mannitol increases renal blood flow and maintains filtration fraction and oxygenation in postoperative acute kidney injury: a prospective interventional study

Gudrun Bragadottir, Bengt Redfors and Sven-Erik Ricksten*

- Bolus dose of mannitol 225 mg/kg (60 CC MANITOL 5%)
- Followed by an infusion at a rate of 75 mg/kg/hour for two 30-minute periods
- Mannitol treatment in these cases increased urine flow by 61% (P <0.001)

- Effects of mannitol (M1, M2)
- vascular resistance (RVR)
- Renal blood flow (RBF)
- Glomerular filtration rate (GFR)
- Renal filtration fraction (FF)

P < 0.05

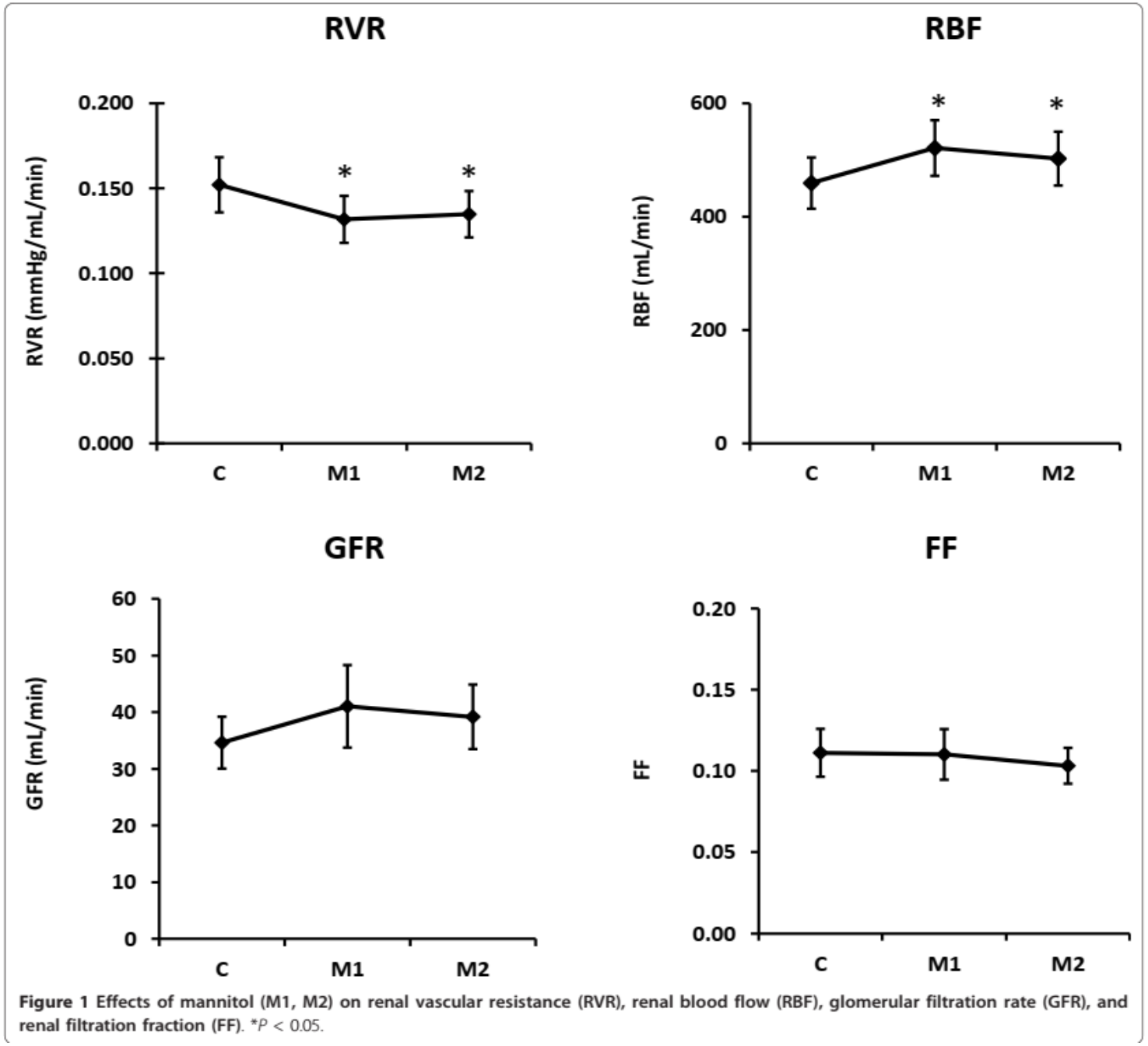

Figure 1 Effects of mannitol (M1, M2) on renal vascular resistance (RVR), renal blood flow (RBF), glomerular filtration rate (GFR), and renal filtration fraction (FF). *$P < 0.05$.

Treatment

Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

- Depend on how severity
  - **Less severe cases can be treated with:**
    - Drinking fluids
    - Getting out of the heat
    - Resting
  - **Moderate to severe cases may need intravenous (IV) fluids and hospital admission.**
    - IV fluids help flush out the muscle proteins and electrolytes.
    - IV fluids can prevent dangerous heart rhythms and loss of kidney function.

Chavez *et al. Critical Care* (2016) 20:135
DOI 10.1186/s13054-016-1314-5

Critical Care

REVIEW Open Access

Beyond muscle destruction: a systematic review of rhabdomyolysis for clinical practice

Luis O. Chavez[1], Monica Leon[2], Sharon Einav[3,4] and Joseph Varon[5*]

Studies included with treatment details

From: Beyond muscle destruction: a systematic review of rhabdomyolysis for clinical practice

Article	Type of study	Population	IV fluid	Bicarbonate/mannitol	Rate of AKI and need for RRT
Altintepe et al. 2007 [55]	CS	*N* = 9	Fluid type used 5 % dextrose and 0.45 NS. 4–8 L of IV fluid daily	40 mEq $NaHCO_3$ and 50 mL of 20 % mannitol mixed with 1 L of IV fluid (0.45 % NaCl and 5 % dextrose) They targeted a urine pH above or equal 6.5	2 patients (28.6 %) developed AKI Patients received hemodialysis due to hyperkalemia
Cho et al. 2007 [56]	PS	*N* = 28	Fluid therapy consisted of lactated Ringer's solution (13 patients) versus NS (15 patients) (the authors concluded that LR was more useful than NS) IV fluid rate 400 mL/h	Bicarbonate was used to achieve urine pH ≥6.5 in the patients with NS IV fluid	No patient developed AKI
Talaie et al. 2008 [51]	RS	*N* = 156	Fluid therapy given 1–8 L in the first 24 h (mean IV fluid 3.2 L/24 h)	Bicarbonate was given to 115 patients	30 patients (28.6 %) developed AKI
Zepeda-Orozco et al. 2008 [57]	RS	*N* = 28	36 % of the patients received saline infusion (20 mL/kg) in the first 24 h	79 % of patients received sodium bicarbonate IV fluid	11 patients (39.2) developed AKI 7 patients with CK levels >5000 U/L required RRT
Sanadgol et al. 2009 [58]	CS	*N* = 31	0.45 % NS	15 mEqL NaHC03 mixed with IV fluid Alkaline IV solution 3–5× more than maintenance rate was used	8 patients (25.8 %) developed AKI
Iraj et al. 2011 [34]	PS	*N* = 638	Authors recommend >6 L/day in severe RM and ≥3 L/day IV fluid in moderate RM to decrease the incidence of AKI	NA	134 patients (21 %) developed AKI 110 patients required RRT

Studies included with treatment details

From: Beyond muscle

Article	Type of study	IV fluid
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Zepeda-Orozco et al. 2008 [57]	RS	36 % of the patients received saline infusion (20 mL/kg) in the first 24 h
Sanadgol et al. 2009 [58]	CS	0.45 % NS
Iraj et al. 2011 [34]	PS	Authors recommend >6 L/day in severe RM and ≥3 L/day IV fluid in moderate RM to decrease the incidence of AKI

Authors fluid therapy suggestion

- Initial fluid infusion rates should be 1 L/h for 2 h after injury
- 500 mL/h after 120 minutes
- These recommendations were not based on randomized clinical trials.
- Patients receiving fluid therapy should be monitored complications
  - Fluid overload
  - Metabolic acidosis

Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

At a hospital, monitor

- Abnormal heart rhythms
- Decreased kidney function
- Seizures
- Elevated compartment pressures
- High potassium levels

Clinical Epidemiology

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ORIGINAL RESEARCH

The Association Between Rhabdomyolysis, Acute Kidney Injury, Renal Replacement Therapy, and Mortality

Clinical Epidemiology 2020:12 989–995

- Cumulative Incidence (Risk) in 1027 Patients with Rhabdomyolysis

	1000–5000 (U/L) (N=828)	5001–15,000 (U/L) (N=161)	15,001+ (U/L) (N=38)
Outcome (95% CI)			
AKI (n=454)	42% (38–45)	44% (36–52)	74% (57–85)
RRT (n=37)	3% (2–5)	4% (2–7)	11% (3–23)
Death (n=168)	17% (14–20)	16% (11–22)	11% (3–23)

Conclusion

- Elevated initial CPK values were associated with an increased risk
  - Acute kidney injury
  - Estimate s of the risk of renal replacement therapy
  - Death were imprecise.

WHAT IS THE CAUSE OF RHABDOMYOSIS IN THIS CASE

CONCOMMITAN
STATIN AND SITAGLIPTIN

Acquired	Hereditary
Extreme physical activity	Metabolic myopathies caused by disorders of:
Influence of extreme temperatures	Fatty acid oxidation
Metabolic disorders of water and salts	Mitochondrial metabolism
Trauma and crush syndrome	Glycolysis/glycogenolysis
Vascular ischemia	Purine nucleotide cycle
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Electrical current	

International Journal of General Medicine

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CASE REPORT

Acute-onset rhabdomyolysis secondary to sitagliptin and atorvastatin interaction

This article was published in the following Dove Press journal:
International Journal of General Medicine
29 April 2016
Number of times this article has been viewed

- A 60-year-old female presented to the emergency room with the chief complaint of chest pain
- Past medical history
  - Hypertension
  - DM
  - Coronary artery disease
  - Hyperlipidemia

Case report (continue)

- She also reported
- Generalized weakness
- Myalgias
- Fever and chills
- Stable vital signs and was otherwise unremarkable
- Trace peripheral edema
- There was no history of recent trauma, crush injury, prolonged immobilization, recent surgery, seizures, drug abuse, or alcoholism

Laboratory workup

- CPK of 13,456 U/L
- Normal troponin-T
- Normal complete blood count
- Creatinine of 1.20 mg/dL
  - GFR = 47 ml/min   EPI- CKD (if stable kidney function)

DRUG HISTORY AND RECOVERY

- Atorvastatin (40 mg)
- Sitagliptin (Januvia® 100 mg)

Sitagliptin and atorvastatin were stopped

- CPK value showed a decreasing trend and was recorded at 1,220 U/L on the day of discharge.

DISCUSSTION

- Sitagliptin is primarily excreted in the urine as the unchanged drug by renal tubular secretion

- About 16% of the drug is excreted as its metabolites and primarily metabolized by CYP3A4, CYP2C8, and P-glycoprotein

- Both atorvastatin and sitagliptin are substrates for CYP3A4 and P-glycoprotein

- The patient developed rhabdomyolysis within a few days after sitagliptin was added which included atorvastatin.

Conclusion

- She did not have any other known etiologies for developing rhabdomyolysis

Drug interaction between atorvastatin and sitagliptin caused toxicity

and rhabdomyolysis

Published in final edited form as:
Diabet Med. 2008 October ; 25(10): 1229–1230. doi:10.1111/j.1464-5491.2008.02536.x.

Renal Failure and Rhabdomyolysis Associated With Sitagliptin and Simvastatin Use

David P Kao, MD, **Holbrook E Kohrt, MD**, and **John Kugler, MD**
Stanford University School of Medicine, Department of Medicine Stanford, CA 94305

- **Case Report**
- a patient with CKD who developed leg pain, weakness, and tenderness
- After starting treatment with high dose sitagliptin while on simvastatin.

Case Report

- A 76 year-old man presented to clinic with 2 weeks of lower extremity pain and weakness
- His medical history included type 2 diabetes mellitus, dyslipidaemia, coronary artery
- He began taking sitagliptin 50 mg daily 6 weeks prior to presentation
- Examination
  - Tenderness and weakness of the proximal muscles in both legs.

Laboratory tests

- Urea 43 mmol/L
- Creatinine 398 µmol/L
- Creatine kinase 22,000 IU/L.

- within 7 days
  - Creatine kinase levels fell
  - His symptoms improved
  - His renal function returned to baseline

Discussion

- Rhabdomyolysis was not reported in clinical trials with sitagliptin
- Rhabdomyolysis is a well documented side effect of statins.
- Maximum serum concentration and terminal half-life of sitagliptin are increased in renal insufficiency
- The patient had tolerated simvastatin and ezetemibe for at least 4 months prior to the onset of symptoms
- Worsening of his renal function, suggesting that this event was precipitated by initiation of sitagliptin therapy

CLINICAL PRACTICE

Clinical Vignettes

Rhabdomyolysis and AKI with Atorvastatin and Sitagliptin Use in the Setting of Low 25-Hydroxyvitamin D Levels

Rupinder Singh Buttar, MD, Jasveen Batra, MD, Jacqueline Kreimerman, BA, Melissa Aleta, MD, and Michal L. Melamed, MD, MHS

Department of Medicine/Nephrology, Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY, USA.

J Gen Intern Med 32(10):1156–9

DOI: 10.1007/s11606-017-4115-x

- An 86-year-old Hispanic woman presented to the emergency department with a chief complaint of generalized weakness and muscle pains for 2 W

- Nausea ,vomiting, diarrhea, yellow skin, dark-colored urine, and light stools.

CLINICAL COURSE

- Generalized weakness and other symptoms developed 1 week after starting sitagliptin and progressively worsened
- Her past medical history
  - Type 2 diabetes mellitus (DM)
  - Hypertension
  - Hyperlipidemia
  - Stage 3 chronic kidney disease (CKD)

Her medications

- Aspirin 81 mg daily
- Atorvastatin 20 mg daily
- Sitagliptin 100 mg daily
- Glipizide 10 mg daily
- Metformin 500 mg twice daily (BID)

The sitagliptin was started 3 weeks prior to presentation

Table 1 Lab Values at Admission and Discharge

Lab test	Admission	Discharge
Sodium (meq/L)	139	138
Potassium (meq/L)	3.6	3.2
Chloride (meq/L)	101	97
Bicarbonate (meq/L)	17	18
Creatinine (mg/dL)	4.44	2.03
BUN (mg/dL)	65	22
CPK (U/L)	13,636	609
Alkaline phosphatase (U/L)	859	574
Bilirubin (mg/dL)	8.3	3.7
SGOT (U/L)	721	182
SGPT (U/L)	261	262
Magnesium (mg/dL)	1.9	1.9
Calcium (mg/dL)	8.9	8.7
Phosphorus (mg/dL)	3.6	3.7
Amylase (U/L)	180	188
Lipase (U/L)	289	132
INR	1.8	1.1
PT (s)	18.2	
PTT (s)	38.7	
25(OH)D (ng/mL)	13.7	27.1 (2 months after discharge)

DIAGNOSTIC APPROCH

- Autoimmune panel that was negative for antinuclear and anti-smooth muscle antibodies
- Cytomegalovirus (CMV)
- Epstein–Barr virus (EBV) tests were negative
- Thyroid-stimulating hormone (TSH) and free T4 test results were normal.

DISCUSSION

Table 2 Case Reports of Rhabdomyolysis from Combining Sitagliptin and Statin Therapies

Case report	Medications	Duration of statin use	Duration of sitagliptin use	Patient baseline characteristics	Medical history	Peak CPK levels	Baseline kidney function
Bhome and Penn 2012[1]	Atorvastatin + sitagliptin	5 years	6 months	75, male, white	Type 2 DM, HTN, dyslipidemia,	10,9710	Normal
Kao et al. 2008[2]	Simvastatin 80 mg + sitagliptin 100 mg	4 months	3 weeks	76, male	Type 2 DM, dyslipidemia, CAD, AF	22,000	Baseline CKD with baseline creatinine 2.3 mg/dL
DiGregorio and Pasikhova 2009[3]	Lovastatin 40 mg + sitagliptin 100 mg	12 years	19 days	75, female, white	Type 2 DM, HTN, dyslipidemia	N/A	N/A
Campos-Davila et al. 2014[4]	Atorvastatin 80 mg + sitagliptin	N/A	N/A	80, male	Type 2 DM, HTN, dyslipidemia, MI, recent stroke	1253	N/A
Current case report	Atorvastatin 20 mg, sitagliptin 100 mg	1 year	3 weeks	86, female, Hispanic	Type 2 DM, HTN, osteoporosis, hypomagnesaemia, dyslipidemia	49,875	Baseline CKD stage 3 (eGFR 50–60)

CONCLUSION

- The co-prescription of statins and sitagliptin is common in patients with type 2 DM and hyperlipidemia.
- This is the fifth report of RM caused by the interaction of a statin with sitagliptin.

Clinicians remain vigilant when using these medications in combination, especially in older patients with underlying CKD.

در تجویز همزمان سیتاگلیپتین و استاتین ها همواره بایستی مراقب تداخل دارویی و افزایش ریسک بخصوص در افراد سالمند و مبتلا به نارسایی کلیه باشیم

Appreciate for your attention