Research Article SLS

# The Effect of Body Mass Index on Patients' Outcomes Following Robotic Distal Pancreatectomy and Splenectomy

Harel Jacoby, MD, Sharona Ross, MD, Iswanto Sucandy, MD, Cameron Syblis, BS, Kaitlyn Crespo, BS, Prakash Vasanthakumar, BS, Michael Trotto, BS, Alexander Rosemurgy, MD

### ABSTRACT

**Background and Objectives:** Obesity has increased over the past decade, yet the correlation among body mass index (BMI), surgical outcomes, and the robotic platform are not well established. This study was undertaken to measure the impact of elevated BMI on outcomes after robotic distal pancreatectomy and splenectomy.

**Methods:** We prospectively followed patients who underwent robotic distal pancreatectomy and splenectomy. Regression analysis was utilized to identify significant relationships with BMI. For illustrative purposes, the data are presented as median (mean  $\pm$  SD). Significance was determined at  $p \leq 0.05$ .

**Results:** A total of 122 patients underwent robotic distal pancreatectomy and splenectomy. Median age was 68  $(64 \pm 13.3)$ , 52% were women, and BMI was 28  $(29 \pm 6.1)$  kg/m<sup>2</sup>. One patient was underweight (<  $18.5 \text{ kg/m^2}$ ), 31 had normal weight ( $18.5-24.9 \text{ kg/m^2}$ ), 43 were overweight ( $25-29.9 \text{ kg/m^2}$ ), and 47 were obese ( $\geq 30 \text{ kg/m^2}$ ). BMI was inversely correlated with age (p = 0.05) but there was no correlation with sex (p = 0.72). There were no statistically significant relationships between BMI and operative duration (p = 0.36), estimated blood loss (p = 0.42), intraoperative complications (p = 0.64), and conversion to open approach (p = 0.74). Major morbidity (p = 0.47), clinically relevant postoperative pancreatic

Digestive Health Institute, Tampa, FL. (all authors)

fistula (p=0.45), length of stay (p=0.71), lymph nodes harvested (p=0.79), tumor size (p=0.26), and 30-day mortality (p=0.31) were related to BMI.

**Conclusion:** BMI has no significant effect on patients undergoing robotic distal pancreatectomy and splenectomy. BMI greater than  $30 \text{ kg/m}^2$  should not defer proceeding with robotic distal pancreatectomy with splenectomy. Limited empirical evidence exists in the literature regarding patients with a BMI greater than  $30 \text{ kg/m}^2$ , and thus any proposed operative intervention should invoke sufficient planning and preparation.

**Key Words:** BMI, Distal pancreatectomy, Obesity, Robotic surgery.

## INTRODUCTION

Minimally invasive surgery has gained acceptance over the past decade as the preferred approach for distal pancreatectomy and splenectomy. Minimally invasive pancreatic surgery was reported in 1996 and over the following years this technique has gradually gained popularity among pancreatic surgeons.<sup>1</sup> Numerous studies comparing the minimally invasive approach (i.e., laparoscopy) to the open approach have shown that the minimally invasive approach has several advantages in perioperative outcomes including less blood loss, lower rate of delayed gastric emptying, fewer postoperative infections, shorter hospital stays, and more rapid return to full functional activity.<sup>2–4</sup>

The application of the robotic platform is relatively nascent in this time, but experience is accumulating and promotes further application. Robotic surgery has marked a new era in minimally invasive surgery. It offers several advantages over conventional laparoscopy including elimination of hand tremor, seven degrees of freedom, excellent ergonomics, high resolution visualization, stable camera, and the ability to perform meticulous and accurate dissection.<sup>5</sup> These advantages enable surgeons to overcome several limitations of traditional laparoscopy and enable a safe and delicate procedure without compromising the oncologic outcomes.<sup>6</sup> Initial reports

Presentation: Oral presentation during Virtual SLS MIS Week, September 23, 2021; Medical Educator Consortium award for best scientific paper.

Acknowledgements: none.

Disclosure: none.

Conflict of interests: Dr. Sharona Ross has educational and research relationships with Intuitive Surgical Inc. (Intuitive Corporation, Sunnyvale, CA)

Funding sources: none

Informed consent: Dr. Sharona Ross declares that written informed consent was obtained from the patient/s for publication of this study/report and any accompanying images.

Address of Correspondence: Dr. Sharona Ross, MD, Digestive Health Institute, Tampa, FL, 33613, Phone: 813-431-3045, E-mail: mysharonaross@gmail.com.

DOI: 10.4293/JSLS.2022.00046

<sup>@</sup> 2023 by SLS, Society of Laparoscopic & Robotic Surgeons. Published by the Society of Laparoscopic & Robotic Surgeons.

describing the implementation of the robotic approach on distal pancreatectomy procedures appeared in the beginning of the current millennium.<sup>7,8</sup> During the following years, a number of studies were published demonstrating superior results compared to laparoscopy, including increased rate of spleen preservation, reduced risk of conversion to an open operation, and shorter length of stay.<sup>9–13</sup>

Obesity is a global concern and has been steadily increasing in recent years. Currently, there are limited data regarding its effect on pancreatic surgery. Previous reports have shown that body mass index (BMI) has been associated with increased risk for new onset diabetes mellitus and increased rates of postoperative pancreatic fistula (POPF) for patients undergoing distal pancreatectomy and splenectomy.14-16 Also, visceral obesity has been reported to be a risk factor in obstructing the view of the surgeon intraoperatively and the development of POPF postoperatively following distal pancreatectomy.<sup>17,18</sup> However, the impact of BMI on patients' outcomes with robotic distal pancreatectomy has hardly been studied.<sup>19</sup> Therefore, based on previous studies describing the effect of BMI on pancreatic operations, in undertaking this study we hypothesized that increased BMI would negatively impact intraoperative and postoperative outcomes for patients undergoing robotic distal pancreatectomy.

## **METHODS**

With Institutional Review Board approval, we prospectively followed 122 consecutive patients who had undergone robotic distal pancreatectomy and splenectomy. Data were collected from November 1, 2012 through June 30, 2020 and included age, sex, BMI, operative time, estimated blood loss (EBL), lymph nodes harvested, intraoperative complications, conversion to open approach, postoperative complications, clinically relevant postoperative pancreatic fistula (CR-POPF), length of stay, tumor size, and 30-day mortality.

BMI was defined as weight (kg) divided by height<sup>2</sup> (meters). It was measured during the week prior to the patient's operation. BMI <  $18.5 \text{ kg/m}^2$  was defined as underweight, BMI of 18.5– $24.9 \text{ kg/m}^2$  was defined as normal weight, BMI of 25– $29.9 \text{ kg/m}^2$  was defined as overweight and BMI ≥  $30 \text{ kg/m}^2$  was defined as obese. Operative time was defined as time from the first incision to the final dressing being placed. Intraoperative complication was defined as an event that had a significant impact on the routine steps of the procedure or diversion from the usual steps of the operation. Postoperative

complication was defined according to the Clavien-Dindo classification as a grade III or above. CR-POPF was defined according to the International Study Group of Pancreatic Fistula as any measurable volume of fluid on postoperative day three or after, with amylase level in drain of three times or more than the upper limit of normal serum amylase, and associated with a clinically relevant condition.<sup>20</sup>

All patients underwent a preoperative assessment by our hepatopancreatobiliary team. This included overall performance status, medical comorbidities, and thorough evaluation of the pancreatic lesion. Advanced imaging with triphasic 1 mm cut abdominal computed tomography (CT) scan and chest CT were obtained to all patients during the month preceding their operation. In addition, abdominal magnetic resonance imaging, magnetic resonance cholangiopancreatography, and endoscopic ultrasound with/without fine needle aspiration was undertaken as needed. All procedures were performed using the da Vinci<sup>®</sup> robotic surgical system (Intuitive Surgical, Sunnyvale, CA). Our surgical technique for robotic distal pancreatectomy and splenectomy was previously described in detail.<sup>12,13</sup>

Data were collected in a secure Microsoft Excel database (Microsoft Corp, Redmond, WA). Statistical analysis was carried out using the GraphPad Prism 8TM software (GraphPad Software Inc., San Diego, CA). Categorial variables were analyzed using the  $\chi^2$  test, continuous variables were analyzed using the independent sample T-test. We used linear regression analyses to compare two continuous variables. *P*-value of < 0.05 was considered statistically significant.

## RESULTS

A total of 122 consecutive patients underwent robotic distal pancreatectomy and splenectomy. The majority of operations (73%) took place between January 1, 2016 through June 30, 2020. Median age was 68 ( $64 \pm 13.3$ ) years, 63 (52%) of them were women. Indication for distal pancreatectomy was adenocarcinoma in 38 (31%) patients, pancreatic cystic neoplasm in 34 (28%) patients, pancreatic neuroendocrine tumor (PNET) in 29 (24%) patients, pseudopapillary neoplasm in 8 (6%) patients and others in 13 (11%) patients. Median BMI was 28 ( $29 \pm 6.1$ ). One patient was underweight, 31 patients (25%) had normal BMI, 43 (35%) patients were overweight, and 47 (39%) patients were obese. BMI was inversely correlated with age; however, there was no correlation between BMI and sex (**Table 1**).

<b>Table 1.</b> Demographic Data Stratified by Body Mass Index						
	Underweight < 18.5	Normal Weight 18.5-24.9	Overweight 25.0-29.9	Obese $\geq 30.0$	Total   <i>P</i> -value	
Number of Patients	1	31	43	47	122	
Age (years)	53	$63(63 \pm 14.7)$	$69(66 \pm 12.4)$	$63(60 \pm 14.1)$	68 (64 ± 13.3)   p = 0.05	
Sex (M/W)	1M	9M/22W	26M/17W	23M/24W	59M/63W   p=0.72	
BMI (kg/m <sup>2</sup> )	17.6	$23(22 \pm 1.9)$	$28(27 \pm 1.5)$	$33(35 \pm 4.5)$	$28(29 \pm 6.1)$	

Table 2.   Intraoperative Variables Stratified by Body Mass Index					
	Underweight < 18.5 (n = 1)	Normal Weight 18.5-24.9 (n=31)	Overweight 25.0-29.9 (n = 43)	Obese $\geq 30.0$ (n = 47)	Total   <i>P</i> -value
Operative Duration (min)	324	222 (228 ± 139.1)	272 (293 ± 139.1)	253 (270 ± 98.5)	243 (269 ± 112.8)   p = 0.36
Estimated Blood Loss (mL)	300	75 (148 ± 175.9)	$100(215 \pm 248.6)$	$100(199 \pm 224.1)$	100 (193 ± 220.5)   p=0.42
Intraoperative Complications (%)	0	0 (0%)	1 (2%)	1 (2%)	2(2%)   p = 0.64
Conversions to 'Open' (n)	1 (100%)	2 (6%)	6 (14%)	3 (6%)	12 (11%)   p=0.71

There were no differences between BMI and operative duration, EBL, intraoperative complications, and conversion to open approach (**Table 2**). Twelve operations (11%) were converted to open approach; however, more than 90% of the conversions occurred during the first 50 operations. The reason for conversion in most of our procedures was tumor invasion to nearby structures including major vessels (e.g. celiac trunk), stomach, and colon. One procedure was converted to due to obesity and accompanying difficulty with dissection.

Overall, we had four (3%) patients who experienced major postoperative complications; two patients had pulmonary complications, one patient had intra-abdominal collection which was drained, and one patient had acute liver failure that progressed to multiorgan failure and death; liver failure occurred for reasons unknow to us. There was no statistical difference between major complication rate and BMI (P = 0.47). There was also no correlation between BMI and CR-POPF, length of stay, tumor size, and lymph node harvested. We had three (2%) postoperative deaths within 30 days, one in a patient of normal weight and two in overweight patients (P = 0.31). Death was due to cardiac arrest, respiratory failure, and multiorgan failure as previously mentioned (**Table 3**).

When analyzing the perioperative variables stratified by sex, it was noted that men were older than women, (70  $(68 \pm 9.6)$  vs. 63  $(59 \pm 16.2)$ , P < 0.001), operative duration was longer for men compared to women (337  $(345 \pm 92.4)$  vs. 231  $(258 \pm 124.8 \text{ minutes})$ , P < 0.001), and lymph nodes harvested were greater for men (10  $(11 \pm 6.1)$  vs. 10  $(9 \pm 4.9)$ , P = 0.05). However, there was no difference between sex and BMI (29  $(29 \pm 5.2)$  vs. 28  $(29 \pm 6.9)$ , p = 1.00) (**Table 4**).

## DISCUSSION

The aim of this this study was to evaluate the impact of BMI on robotic distal pancreatectomy and splenectomy. Given that high BMI has previously been found to be a poor prognostic factor in open and laparoscopic distal pancreatectomy and splenectomy, we assumed that robotic approach would yield similar results.<sup>14,15</sup> However, the results of this study show that BMI had no meaningful effect on intraoperative and postoperative outcomes. To our knowledge, this is one of the largest studies of a single institution's experience of robotic distal pancreatectomy and splenectomy, and one of the even fewer that examined the association between this approach and BMI.

The Effect of Body Mass Index on Patients' Outcomes Following Robotic Distal Pancreatectomy and Splenectomy, Jacoby H et al.

<b>Table 3.</b> Postoperative Data Stratified by Body Mass Index					
	Underweight < 18.5 (n = 1)	Normal Weight 18.5-24.9 (n = 31)	Overweight 25.0-29.9 (n=43)	Obese ≥ 30.0 (n = 47)	Total   <i>P</i> -value
Major Complications (%)	1 (100%)	0	1 (2%)	2 (4%)	4 (3%)   p=0.47
CR-POPF (%)	0	0	3 (7%)	1 (2%)	4 (3%)   p = 0.45
Length of Stay (Days)	18	$4(4 \pm 1.2)$	$4(5 \pm 3.2)$	$4(5 \pm 2.8)$	$4(5 \pm 3.0) \mid p = 0.71$
Tumor Size (cm)	6.5	3 (4 ± 2.6)	$3(4 \pm 3.4)$	$3(4 \pm 3.4)$	$3(4 \pm 2.8) \mid p = 0.26$
Lymph Nodes Harvested (n)	21	$10(10 \pm 4.4)$	$9(10 \pm 5.4)$	$10(10 \pm 6.2)$	10 (10 ± 5.6)   p = 0.79
30-Days Mortality (n)	0	1 (3%)	2 (5%)	0	3 (2%)   p = 0.31
Abbreviations: CR-POPF, clinic	ally relevant postop	erative pancreatic fi	stula.		

	<b>Table 4.</b> Perioperative Data Stratified b	y Sex	
	Men	Women	<i>P</i> -value
Number of Patients	59	63	
Age (years)	$70(68 \pm 9.6)$	$63(59 \pm 16.2)$	< 0.001
BMI (kg/m <sup>2</sup> )	$29(29 \pm 5.2)$	$28(29 \pm 6.9)$	1.00
Operative Duration (min)	$337(345 \pm 92.4)$	$231(258 \pm 124.8)$	< 0.001
EBL (mL)	$100(192 \pm 208.5)$	$100(194 \pm 232.8)$	0.96
Intraoperative Complications (%)	1 (2%)	1 (2%)	1.00
Conversions to 'Open' (n)	7 (12%)	5 (8%)	0.55
Postoperative Complications (%)	3 (5%)	1 (2%)	0.35
CR-POPF (%)	3 (5%)	1 (2%)	0.35
Length of Stay (days)	$4(6 \pm 3.4)$	$4(5 \pm 2.3)$	0.06
Tumor Size (cm)	$3(4 \pm 2.4)$	$3(4 \pm 3.1)$	0.06
Lymph Nodes Harvested (n)	$10(11 \pm 6.1)$	$10(9 \pm 4.9)$	0.05
30-Days Mortality (n)	2 (3%)	1 (2%)	0.52

Most of our patients were women in their 60's who were overweight or obese. BMI was inversely correlated with age, as older patients had a trend for lower BMI (P =0.05). We think that this result is more of a type 1 error than a meaningful finding. We found no association between BMI and intraoperative variables. High BMI was previously recognized to prolong the operation time in open and laparoscopic distal pancreatectomy and splenectomy. In addition, operations in obese patients had higher blood loss and a higher conversion rate compared to patients with normal BMI.<sup>21</sup> In the study of Nassour I, et al., BMI was found to be an independent risk factor during laparoscopic distal pancreatectomy with 17.3% conversion rate.<sup>22</sup> However, using the robotic platform we were able to generate a lower conversion rate of 11%, with more than 90% of our conversions occurring during the first 50 operations, denoting a rapid learning curve. We encountered only one operation that had to be converted to open approach due to obesity alone. We estimate that the robotic platform enabled us to overcome technical difficulties caused by the excess intra-abdominal fat.

Our major complication rate was 3%. This is lower compared to other studies, both in open and minimally invasive distal pancreatectomy, which stands at a range of 7%-20%.4,11 BMI had no impact on major morbidity. We were able to maintain a low rate of CR-POPF with less than a handful. Although all patients with CR-POPF were either overweight or obese, there was no significant relationship between BMI and occurrence of CR-POPF. Previous studies comparing the impact of BMI on distal pancreatectomy reported that obesity is associated with higher rate of POPF.<sup>14,16</sup> While it is well established that patients with an elevated BMI have softer and fattier pancreatic tissue and therefore a higher rate of pancreatic fistula, we think that there are several explanations to our results: First, we use the robotic stapler to transect the pancreas. This stapler has the advantage of monitoring the tissue compression before firing and making automatic adjustments to the firing process. During the firing process, if the compression is insufficient, it pauses for additional compression until full compression is obtained. Second, we always reinforce the pancreatic stump with running polypropylene suture, folding the pancreatic edge down onto dorsal retroperitoneal soft tissue, using the tissue as a buttress. We use a continuous nonabsorbable unidirectional barbed suture and perform this tight enough on one hand, but with sufficient spacing between sutures on the other hand to prevent ischemia on the pancreatic edge, which may end with pancreatic ischemia and subsequent leakage. And third, using the robotic system that includes a high-quality three-dimensional camera and excellent articulation capabilities, identifying all structures more clearly, performing a superior meticulous dissection, and avoiding unnecessary manipulations in the pancreas are all possible. Despite this, since all patients with CR-POPF were overweight or obese, a larger study group might have found a statistical difference. Length of hospital stay was not affected by BMI and was considerably shorter than other series.<sup>23</sup>

We stratified our perioperative results by sex, since men have higher amount of abdominal visceral fat compared to women, who have more subcutaneous fat.<sup>24</sup> While visceral fat poses a surgical challenge in minimally invasive operations, subcutaneous fat has minimal effect. Early in our experience we believed that robotic distal pancreatectomy and splenectomy could be more challenging when the patients were men, in part because of increased visceral fat, and sex and visceral fat content might affect postoperative outcomes. Our results show that operative time was longer for men compared to women (337 (345 ± 92.4) vs. 231 (258 ± 124.8), P < 0.001). However, there were no statistical differences regarding the postoperative results except the number of lymph nodes that were harvested, which were surprisingly higher, but uncertainly meaningful in men (10 ( $11 \pm 6.1$ ) vs. 10 ( $9 \pm 4.9$ ), P = 0.05). It is also worth noting that the mean age of the men was almost a decade older than the women.

An alternative reasoning for lack of association between BMI and postoperative outcomes could be due to inadequate sample size. Though to our knowledge this is the largest study to investigate the relationship between BMI and distal pancreatectomy, our study includes only 122 patients. For a study that would have a confidence level of 95% and a margin of error of  $\pm$  5%, a population size of 385 patients would be necessary.

In conclusion, our results demonstrate that BMI has no significant effect on patients undergoing robotic distal pancreatectomy and splenectomy. Further studies are necessary to understand the full impact of obesity on patients undergoing robotic distal pancreatectomy and splenectomy, and to determine whether the robotic system has an advantage over other alternatives.

#### **References:**

1. Underwood R, Soper N. Current status of laparoscopic surgery of the pancreas. *J Hepatobiliary Pancreat Surg.* 1999;6 (2):154–164.

2. Tran Cao HS, Lopez N, Chang DC, et al. Improved perioperative outcomes with minimally invasive distal pancreatectomy: results from a population-based analysis. *JAMA Surg.* 2014;149 (3):237–243.

3. de Rooij T, van Hilst J, van Santvoort H, et al. Minimally Invasive Versus Open Distal Pancreatectomy (LEOPARD): a multicenter patient-blinded randomized controlled trial. *Ann Surg.* 2019;269(1):2–9.

4. Song SH, Kim HJ, Park EK, Hur YH, Koh YS, Cho CK. Comparison of laparoscopic versus open distal pancreatectomy for benign, pre-malignant, and low grade malignant pancreatic tumors. *Ann Hepatobiliary Pancreat Surg.* 2020; 24(1):57–62.

5. Giulianotti PC, Coratti A, Angelini M, et al. Robotics in general surgery: personal experience in a large community hospital. *Arch Surg.* 2003;138(7):777–784.

6. Hong S, Song KB, Madkhali AA, et al. Robotic versus laparoscopic distal pancreatectomy for left-sided pancreatic tumors: a single surgeon's experience of 228 consecutive cases. *Surg Endosc.* 2020;34(6):2465–2473.

7. Griffin JF, Poruk KE, Wolfgang CL. Pancreatic cancer surgery: past, present, and future. *Chin J Cancer Res.* 2015;27 (4):332–348. 8. Ryan CE, Ross SB, Sukharamwala PB, Sadowitz BD, Wood TW, Rosemurgy AS. Distal pancreatectomy and splenectomy: a robotic or less approach. *JSLS*. 2015;19(1):e2014.00246.

9. Guerrini GP, Lauretta A, Belluco C, et al. Robotic versus laparoscopic distal pancreatectomy: an up-to-date meta-analysis. *BMC Surg.* 2017;17(1):105.

10. Zhou JY, Xin C, Mou YP, et al. Robotic versus laparoscopic distal pancreatectomy: a meta-analysis of short-term outcomes. *PLoS One.* 2016;11(3):e0151189.

11. Daouadi M, Zureikat AH, Zenati MS, et al. Robot-assisted minimally invasive distal pancreatectomy is superior to the laparoscopic technique. *Ann Surg.* 2013;257(1):128–132.

12. Rosemurgy AS, Luberice K, Krill E, et al. 100 robotic distal pancreatectomies: the future at hand. *Am Surg.* 2020;86(8):958–964.

13. Ross S, Rayman S, Sucandy I, Syblis C, Rosemurgy A. Whipple's operation and distal pancreatectomy. In: Costello T, *Principles and Practice of Robotic Surgery*. CH: Elsevier, In press.

14. Peng YP, Zhu XL, Yin LD, et al. Risk factors of postoperative pancreatic fistula in patients after distal pancreatectomy: a systematic review and meta-analysis. *Sci Rep.* 2017;7(1):185.

15. Dai M, Xing C, Shi N, et al. Risk factors for new-onset diabetes mellitus after distal pancreatectomy. *BMJ Open Diab Res Care*. 2020;8(2):e001778.

16. Zhou Y, Drake J, Deneve JL, et al. Rising BMI is associated with increased rate of clinically relevant pancreatic fistula after distal pancreatectomy for pancreatic adenocarcinoma. *Am Surg.* 2019;85(12):1376–1380.

17. Hanna EM, Rozario N, Rupp C, Sindram D, Iannitti DA, Martinie JB. Robotic hepatobiliary and pancreatic surgery; lessons learned and predictors for conversion. *Int J Med Robot.* 2013;9(2):152–159.

18. Vanbrugghe C, Ronot M, Cauchy F, et al. Visceral obesity and open passive drainage increase the risk of pancreatic fistula following distal pancreatectomy. *J Gastrointest Surg.* 2019;23 (7):1414–1424.

19. Wang SE, Daskalaki D, Masrur MA, Patton K, Bianco FM, Giulianotti PC. Impact of obesity on robot-assisted distal pancreatectomy. *J Laparoendosc Adv Surg Tech A*. 2016;26(7):551–556.

20. Bassi C, Marchegiani G, Dervenis C, et al. The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 tears after. *Surgery.* 2017; 161(3):584–591.

21. Sahakyan MA, Røsok BI, Kazaryan AM, et al. Impact of obesity on surgical outcomes of laparoscopic distal pancreatectomy: a Norwegian single-center study. *Surgery*. 2016;160(5):1271– 1278.

22. Nassour I, Wang SC, Porembka MR, et al. Conversion of minimally invasive distal pancreatectomy: predictors and outcomes. *Ann Surg Oncol.* 2017;24(12):3725–3731.

23. Chen S, Zhan Q, Chen JZ, et al. Robotic approach improves spleen-preserving rate and shortens postoperative hospital stay of laparoscopic distal pancreatectomy: a matched cohort study. *Surg Endosc.* 2015;29(12):3507–3518.

24. Tchernof A, Després JP. Pathophysiology of human visceral obesity: an update. *Physiol Rev.* 2013;93(1):359–404.