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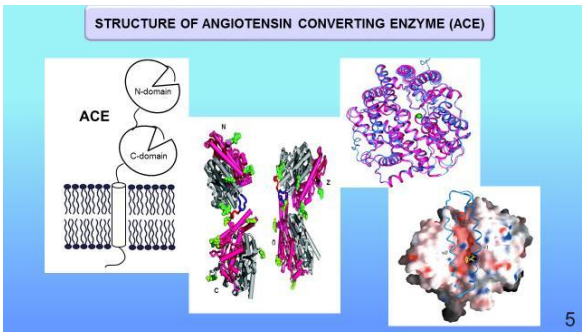
Research Paper



Screening of Novel Angiotensin I Converting Enzyme Inhibitory Peptides Derived From Enzymatic Hydrolysis of Salmon Protamine.

Rasyad F, Huang TC, Hsu JL, Fadjar M.
J. Life Sci. Biomed., 6 (5): 100-105, 2016;
pii:S225199391600017-6

Abstract
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Keywords: Angiotensin I Converting Enzyme (ACE), Antihypertensive, Bioactive Peptide, Chum Salmon (*Oncorhynchus keta*), Enzymatic hydrolysate, Salmon Protamine

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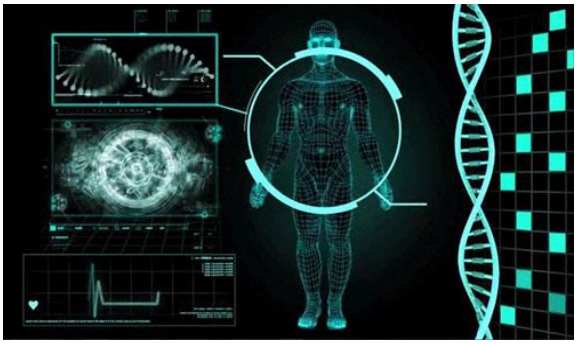
Review



On the Physiology and Medicine of Aging.

Pandit A, Pandey Bahuguna D, Kumar Pandey A, Pandey BL.
J. Life Sci. Biomed., 6 (5): 106-114, 2016;
pii:S225199391600018-6

Abstract
World-over the population of aged is steadily increasing and physiology and medicine of aging constitute major biomedical concern. Evolutionary understanding of biology has given rise to multiple diverse causal theories of aging, with different extents of scientific validation. Genetic coding of life span has not been tenable, although the gene-environment interactions seem to heavily bear upon the phenomenon. Visibly, aging involves structural and functional erosion undermining efficient bodily readjustments to the demands of changing life environments. Age associated diseases indicate imbalance in energy intake and expenditure. Healthy process of ageing must be impacted by the same to acquire undesirable forms and rate of progression. Aberrations in lifestyle and nutrition prominently link to pathogenesis of age associated diseases, and provide objects for preventive and corrective interventions. Treading on such very frame, the physiologic and medical understanding of the ageing process, is herein, developed with a degree of over-simplification. The current understanding on biological factors of aging is reviewed emphasizing the interrelation among them, to contemplate personalized preventive and mitigative interventions.

Keywords: Biology of ageing; Physiology of ageing; Mechanisms of ageing; Ageing prevention; Medical management of ageing.

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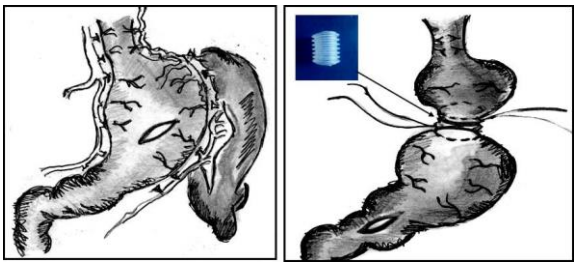
Research Paper



Results of Gastroesophageal Collector Modified Total Dissociation in Patients with Portal Hypertension.

Nazyrov FG, Devyatov AV, Babadjanov AKh and Ruziboev SA.
J. Life Sci. Biomed., 6 (5): 115-119, 2016;
pii:S225199391600019-6

Abstract
The purpose of research was to study long-term results of the modified technique of gastroesophageal collector total dissociation (GECTD) in patients with portal hypertension. Materials and methods. Currently a modified version of the operation has been performed in 73 patients with the portal hypertension (PH) syndrome. In 36 patients the cause of PH was liver cirrhosis, 30 patients were diagnosed with extrahepatic form of PH, mixed form of PH was determined in 8 patients. The age of patients ranged from 13 to 65 years, thus the median was 31.6 ± 1.7 years. Patients randomizing by gender was as follows: men - 44, women - 29. In 53 cases patients were admitted in a planned order, and 20 patients were delivered urgently with the clinical picture of gastroesophageal bleeding. Results and discussion remote period was followed up in 46 patients with primary procedure and in 66 patients with a modified technique of GECTD. Rebleeding was observed in 15.2% of patients, 6.5% on the background of anastomositis. Gastrostasis occurrence was detected in 3 of 46 patients. Liver failure occurred in 23.9% of patients, 15.2% patients died on the background of these complications. In the group with a modified procedure bleeding was observed in 6.0% cases. Bleedings from erosion in the area of ligature transection were stopped conservatively. Mortality in long-term period of observation was 7.6% (5 patients). Overall mortality for the near and distant periods in the comparison groups was 22.2% and 16.4%, respectively. Conclusion – dissociation of gastroesophageal venous reservoir by ligature transection on synthetic prosthesis, unlike previously proposed methods of GECTD allows not only to ease technique of operation, but also provides prevention of early postoperative complications associated with traumatism of previous methods, as well as the stomach gross functional disorders in the long term period.

Keywords: Liver Cirrhosis, Portal Hypertension, Dissociative Operations, Technique of Ligature Transection, Bleeding from Esophageal Varices

[Full text-PDF] [XML]

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Screening of Novel Angiotensin I Converting Enzyme Inhibitory Peptides Derived From Enzymatic Hydrolysis of Salmon Protamine

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ABSTRACT: Angiotensin I converting enzyme (ACE) inhibitory peptide is widely recognized as useful therapeutic approach in the treatment of hypertension. Bioactive peptides from natural sources, including marine fish, are more considered because it has no harm effects. The objective of this study is screening the presence of potential ACE inhibitory peptide from salmon protamine. ACE inhibitory peptide was purified from salmon protamine after 16 hours of hydrolysis by various enzymes and centrifuged using 3 kDa molecular weight cut off (MWCO) ultrafiltration membrane. The peptide sequences were analyzed by Liquid Chromatography Tandem Mass Spectrometric (LC-MS/MS). ACE inhibitory activity was measured using Reversed-Phase High-Performance Liquid Chromatography (RP-HPLC). The results indicated that trypsin hydrolysate had the highest ACE inhibitory activity compared to the other hydrolysates with IC_{50} value 135.96 µg/ml. LC-MS/MS analysis of tryptic protamine identified two major peaks with three peptide sequences, Ser-Ser-Arg-Pro-Ile-Arg (SR-6), Ser-Ser-Ser-Arg-Pro-Ile-Arg (SR-7), Pro-Arg-Arg-Ala-Ser-Arg (PR-6) which sourced from salmine of Chum Salmon (*Oncorhynchus keta)*. The ACE inhibitory peptides from Salmon Protamine still has not been reported previously, therefore it can be beneficial for preventing hypertension.

Author Keywords: Angiotensin I Converting Enzyme (ACE), Antihypertensive, Bioactive Peptide, Chum Salmon (*Oncorhynchus keta*), Enzymatic hydrolysate, Salmon Protamine

ORIGINAL ARTICLE
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INTRODUCTION

Nowadays, the inhibition of ACE activity is commonly known as a functional therapeutic agent for preventing and curing hypertension. It has been in use for the last two decades and the tendency to use them will be continuously increased [1]. Currently, several synthetic antihypertensive drugs based on ACE inhibitors have been clinically used such as captopril, enalapril, alcacepril, and lisinopril [2]. Even though these synthetic ACE inhibitors could be possibly utilized as antihypertensive drugs, unfortunately they still have some undesirable side effects such as coughing, allergic reactions, taste disturbance, and skin rashes [3]. Thus, developments and investigations to explore a beneficial and economical ACE inhibitors are required to prevent hypertension.

One of the most popular and favorite fish in the world is Salmon. It is considered to be healthy due to its high nutritional value and pharmacological activity. Previous studies have investigated ACE inhibitory peptides from Salmon by-product such as fillet and residuals [4], skin [5, 6], and pectoral fin [7]. However, the ACE inhibitory peptides from Salmon Protamine still has not been reported.

The objectives of this study were to hydrolysis protein using different proteases, and the protein hydrolysate was assessed for bioactivity including angiotensin converting enzyme (ACE) inhibitory activity. Furthermore, the sequences of the bioactive peptides were determined by LC-MS/MS [8].

MATERIALS AND METHODS

Salmon Protamine were treated with a single protease, with an enzyme to protein ratio of 1:50 (w/w) using different temperatures which were based on the enzymes' activities: trypsin (37 °C), α-chymotrypsin (37 °C), pepsin (37 °C), and thermolysin (60 °C). The enzymatic digestions of the salmon protamine were kept at pH 8, except for pepsin, which was adjusted to pH 1.3. After incubation for 16 hours, the hydrolysis was stopped by centrifugation at low temperature (14,000 rpm, 10 min, 4 °C) in ultrafiltration membrane (3 kDa MWCO). The filtrate (<3 kDa) was lyophilized and kept at −20 °C for further assay or analysis.

The ACE inhibitory activity was determined according to the method reported by Cushman et al [9] with partial modification. The sample solution containing 30 µl of 2.5 mM hippuryl-L-histidyl-L-leucine (HHL) as a substrate and 10 µl of inhibitor (at an indicated concentration) in 200 mM borate buffer containing 300 mM NaCl (adjusted to pH 8.3) was pre-incubated at 37 °C for 5 minutes. The control solution was prepared using the same buffer but without inhibitor. Afterwards, 20 µl of 2 mU/ml ACE in 200 mM borate buffer was added to the sample solution and control solution, individually. The reaction mixture was incubated statically at 37 °C for 30 minutes and then shaken in a thermostatically controlled shaker incubator (200 rpm) at 37 °C for 30 minutes. The reaction was quenched under acidic conditions by adding 1 M HCl (60 µl). Ferulic acid 0.2 mg/ml (10 µl) was used as an internal standard for normalizing variation derived from different samples. HHL and its hydrolyzed product, hippuric acid (HA) were analyzed using an HPLC equipped with a C_{18} column. The resulting HA was detected using a UV detector fixed at 228 nm. The ACE inhibition (%) was determined based on the following equation:

$$[1-(\Delta A_{inhibitor}/\Delta A_{control})] \times 100$$

where ΔAinhibitor was the peak area of HA in the reaction mixture by the presence of peptide as ACE inhibitor and ΔAcontrol was the peak area of HA in the reaction mixtures without peptide as ACE inhibitor. Definition of ACE activity: One unit (U) of ACE activity was defined as the amount of enzyme required to catalyze formation of 1 µmol of HA from HHL per minute at 37 ^{0}C.

The peptide sequences in the lyophilized hydrolysate were further identified using LC-MS/MS analysis and database matching. Freeze dried peptides were dissolved in 5% ACN (Acetonitrile) and 0.2% FA (Ferulic acid) in deionized water for LC–MS/MS analysis. LC–MS/MS analysis was performed using a Thermo LCQ DECA XP MAX system with an electrospray ionization (ESI) source (Thermo Scientific Inc., USA). Samples were loaded onto a BioBasic C_{18} column with diameter 150 × 2.1 mm, particle size 5 µm. The mobile phase consisted of Solution A (100% deionized water and 0.1% FA) and Solution B (100% ACN and 0.1% FA) and was kept at a flow rate of 200 µl/min. The MS/MS raw data were acquired using Thermo-XCalibur™ Thermo-Scientific) then processed into MGF files using Mascot Distiller v2.3.2.0 (Matrix Science, London, UK). The resulting MGF files were searched using the Mascot search engine v2.3 (Matrix Science, UK).

RESULTS AND DISCUSSIONS

ACE inhibitory activity of each hydrolysates is shown in Figure 1. Captopril is used as positive control. All hydrolysates have potential to inhibit ACE, but compared to other hydrolysates, the highest inhibition was shown in tryptic hydrolysate with 94.82% followed by chymotrypsin, thermolysin and pepsin with the inhibition of 79.11%, 70.20%, 48.66% respectively.

Tryptic hydrolysate, because it has the highest ACE inhibition, further was analyzed for IC_{50} of ACE inhibition activity. The IC_{50} or the half maximal inhibitory concentration represents the concentration of a peptide that is required for 50% inhibition of its target enzyme. To find out the IC_{50} value of crude hydrolysates, the relative ACE inhibition was first determined for various concentrations of peptide; afterwards, the IC_{50} was evaluated by plotting the curves of relative ACE inhibition against six different peptide concentrations (Figure 2).

The IC_{50} value of tryptic hydrolysate was considered as a low inhibition. The low IC_{50} value may be due to cumulative and synergistic effects of various active peptides present in each hydrolysate [10].

To characterize the peptide identities, the lyophilized tryptic hydrolysate was subjected into LC-MS/MS for analysis of ACE inhibitory peptides. Two major peaks were observed in the LC-MS chromatogram. Through LC–MS/MS analysis and database-assisted identification, peptides derived from Salmon Protamine are compared to the predicted peptides forecasted by peptide sequence application. All the sequences are summarized in Table 1.

LC-MS/MS analysis indicated two major peaks with three peptide sequences. A peptide was located at the first peak with retention time at minute 1.74, whereas two other peptides were located at the second peak with retention time at minute 10.70 and 10.95 respectively. Based on Mascot Distiller database search, for triply

charged the peptide with m/z at 247.91 was identified as Pro-Arg-Arg-Ala-Ser-Arg (PRRASR), for doubly charged the peptide with m/z at 358.60 as Ser-Ser-Arg-Pro-Ile-Arg (SSRPIR) and m/z at 402.03 as Ser-Ser-Ser-Arg-Pro-Ile-Arg (SSSRPIR).

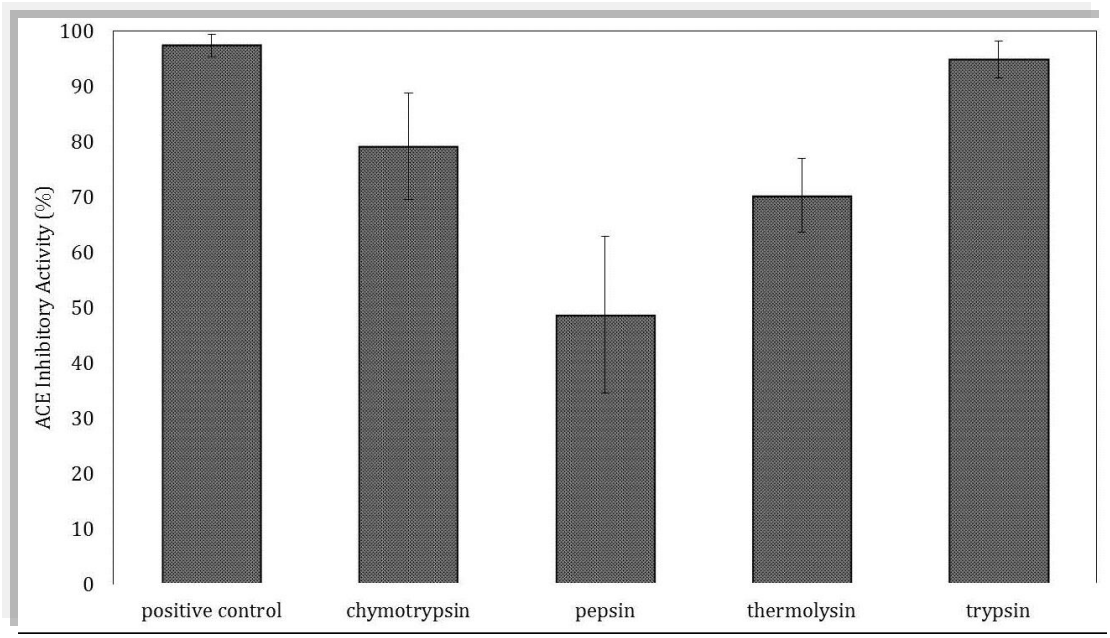

Figure 1. ACE inhibitory activities of enzymatic hydrolysates from Salmon Protamine.

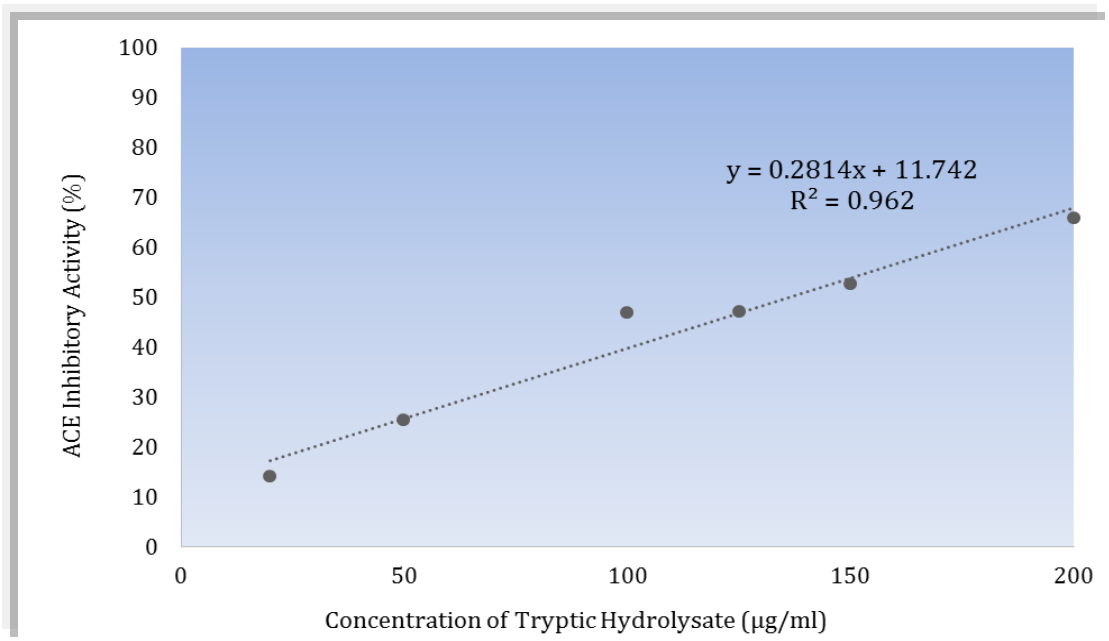

Figure 2. IC_{50} of tryptic hydrolysate from salmon protamine.

Table 1. Comparison of tryptic hydrolysate and predicted tryptic peptide sequences.

Tryptic Hydrolysate Peptides			Predicted Tryptic Peptides		
m/z	**Position**	**Sequence**	**m/z**	**Position**	**Sequence**
802.0454	6-12	SSSRPIR	802.4530	6-12	SSSRPIR
715.1854	7-12	SSRPIR	428.2728	15-17	RPR
740.9328	16-21	PRRASR	333.1881	19-21	ASR

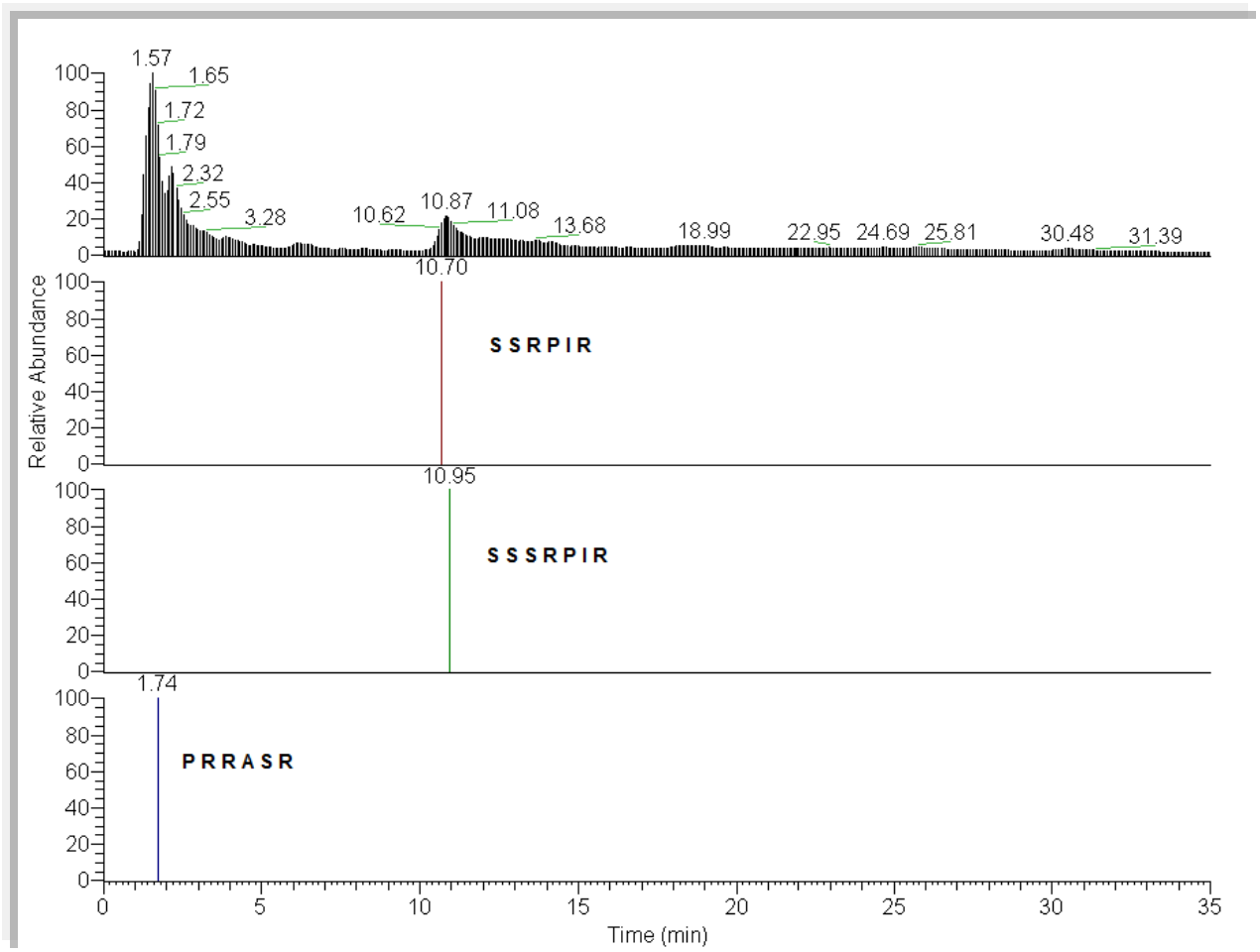

Figure 3. LC-MS chromatogram of tryptic hydrolysate

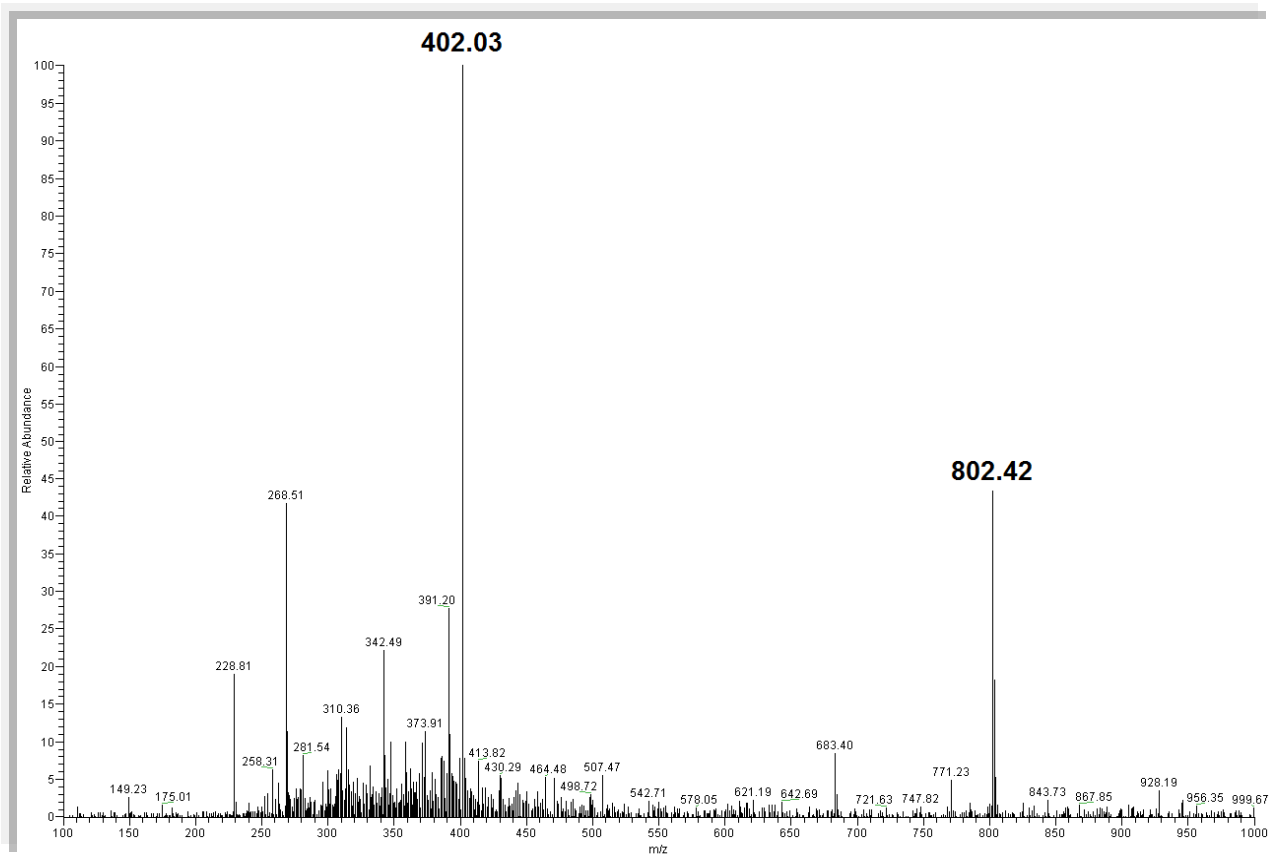

Figure 4. LC-MS chromatogram of peptide SSSRPIR

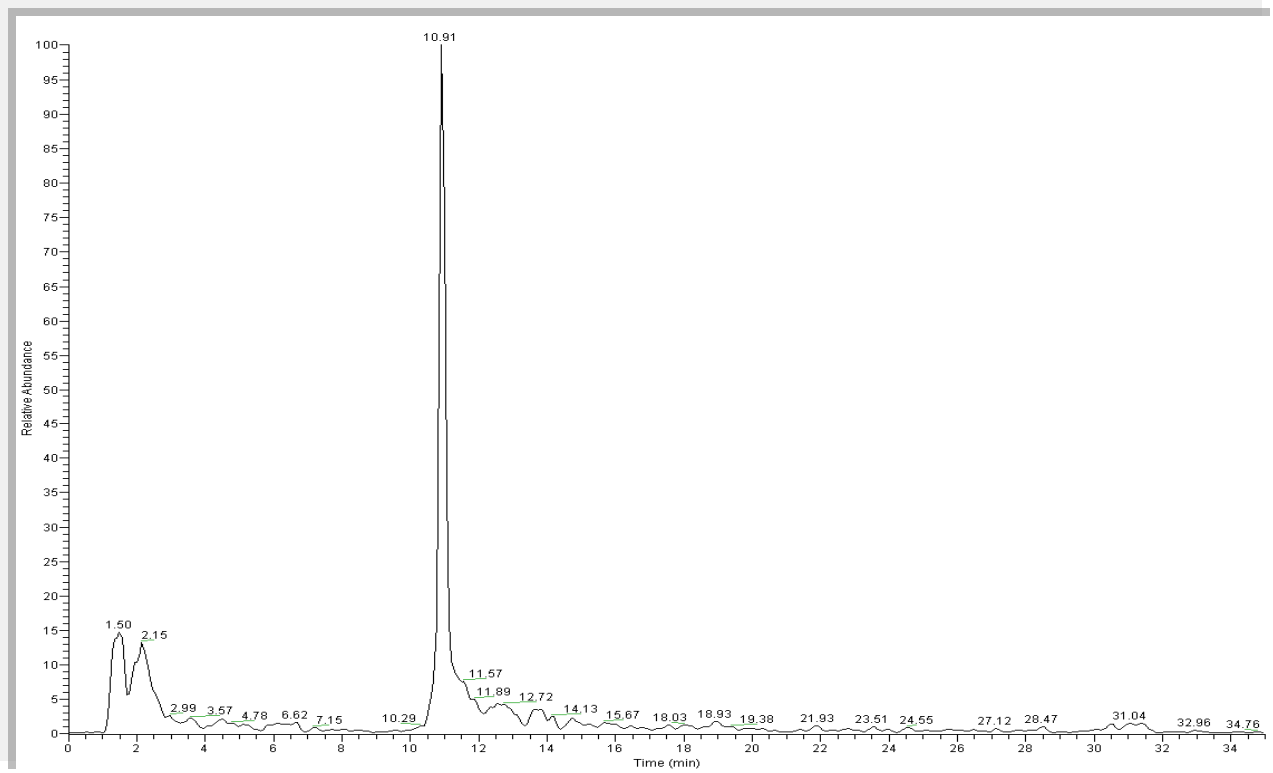

Figure 5. Mass spectrum of peptide with m/z 402.03 for doubly charged and m/z 802.42 for singly charged.

Recently, salmon protamine widely used for pharmaceutical excipients. This cationic peptide derived from salmon milt. Protamine itself has a molecular mass of approximately 4000 Da with about 70% of the basic amino acid arginine. Basically, protamines belong to a diverse protein family of arginine rich peptides. Peptides derived from protamine could be useful to observe the differential in vitro antimicrobial activity of a 12-residue-long arginine-rich peptide and examined against bacterial and parasite microbes. Protamine C-terminal fragment can be utilized as a potential new antimicrobial peptide [11].

In addition to medical and antimicrobial use, Salmon Protamine is also expected could be used as antihypertensive agent. Higher level of arginine can be investigated for hypertension therapy. Since the arginine-rich peptides also exhibited moderate *in vitro* ACE and renin inhibitory activities, it is also possible that more than one mechanism was involved in producing the antihypertensive effects [12].

Digestion of salmon protamine by various digestive enzymes has resulted the release of bioactive peptides. Chymotrypsin, pepsin, thermolysin and trypsin are some of commonly used and widely distributed commercial enzymes. According to the result of this research, tryptic hydrolysate of salmon protamine has the highest ACE inhibitory activity. It indicated that bioactive peptides hydrolysis strongly affected by protease. Trypsin is widely used to produce ACE inhibitory peptides. However, other proteinases (chymotrypsin, pepsin, thermolysin) as well as enzymes from bacterial and fungal sources have been utilized to generate bioactive peptides [13].

CONCLUSION

Angiotensin I Converting Enzyme (ACE) Inhibitory peptides were screened from enzymatic hydrolysis of salmon protamine using various enzymes. Tryptic hydrolysate has the highest ACE inhibitory activity. LC-MS/MS analysis of tryptic protamine identified two major peaks with three peptide sequences, Ser-Ser-Arg-Pro-Ile-Arg (SR-6), Ser-Ser-Ser-Arg-Pro-Ile-Arg (SR-7), Pro-Arg-Arg-Ala-Ser-Arg (PR-6) which sourced from salmine AII of Chum Salmon (*Oncorhynchus keta)*. According to this study, it can be concluded that bioactive peptide derived from salmon protamine has a potential ACE inhibitory peptide. Further study of ACE inhibitory peptide from Salmon protamine and the antihypertensive effect on spontaneous hypertensive rat (SHR) is highly needed in order to discover a new innovation in the treatment of hypertension.

Competing interests

The authors declare that they have no competing interests.

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On the Physiology and Medicine of Aging

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ABSTRACT: World-over the population of aged is steadily increasing and physiology and medicine of aging constitute major biomedical concern. Evolutionary understanding of biology has given rise to multiple diverse causal theories of aging, with different extents of scientific validation. Genetic coding of life span has not been tenable, although the gene-environment interactions seem to heavily bear upon the phenomenon. Visibly, aging involves structural and functional erosion undermining efficient bodily readjustments to the demands of changing life environments. Age associated diseases indicate imbalance in energy intake and expenditure. Healthy process of ageing must be impacted by the same to acquire undesirable forms and rate of progression. Aberrations in lifestyle and nutrition prominently link to pathogenesis of age associated diseases, and provide objects for preventive and corrective interventions. Treading on such very frame, the physiologic and medical understanding of the ageing process, is herein, developed with a degree of over-simplification. The current understanding on biological factors of aging is reviewed emphasizing the interrelation among them, to contemplate personalized preventive and mitigative interventions.

Author Keywords: Biology of ageing; Physiology of ageing; Mechanisms of ageing; Ageing prevention; Medical management of ageing.

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REVIEW

INTRODUCTION

Aging is inevitable phenomenon of biology, driven by multiple factors at varied rates and fashion in different species and even among members of same species. As per the Darwinian principle, successful attainment of reproductive age is minimum essential life span for species [1]. Extended living beyond essential life span results in accumulating damages in biochemical architecture of body comprised of nucleic acids, proteins and lipids. A progressive failure of homeostasis and homeodynamics manifests at different levels of functional organization, worsening in to disease forms and may cause eventual death. The failures of repair and maintenance mechanisms are central to mechanistic principle of aging [2].

Genes and Aging

Finite genetic basis for aging is unconceivable. Consensus is evolving over crucial contribution of threshold changes in epigenetic mechanisms to aging process and absence of any evolving superior repair mechanisms to avert aging. Aging studies in the centenarians, suggest role of human leukocyte antigen (HLA), alleles on specific chromosome loci and also of varied alleles of APOA and APOB genes coding for apolipoproteins A and B, and angiotensin converting enzyme genotype in conferring longevity [3]. Discovery of Klotho (KL) gene encoding α-klotho protein, has helped advancing understanding of ageing process. α- klotho protein is multifunctional and regulates metabolism of phosphates, calcium and vitamin D. Mutation of KL gene are associated with hypertension and kidney disease suggesting renal function as their prime target. In mice, klotho gene functions as ageing suppressor gene, extending life span upon over-expression and to cause accelerated ageing phenotype, when disrupted [4]. α klotho protein antagonizes a bone derived hormone that inhibits renal vitamin D3 biosynthesis, also suppress insulin and Wnt signaling pathways, inhibits oxidative stress and regulates phosphate and calcium absorption [5]. These proteins locate on renal tubule cell membrane and shed fragments in

circulation. The later interact with signaling pathways of multiple growth viz.insulin/ insulin like growth factor 1(IGF1), Wnt etc. and activity of several ion channels. The protein appears to also protect cells from oxidative stress [6]. Humanin is a mitochondria associated peptide that plays role in cell metabolism, survival, response to stress, inflammation and apoptosis. Humanin analogues favourably influence age related diseases. Association between human in levels and growth hormone/IGF1 axis and life span has also been demonstrated in mice [7].

Developmental ontogeny of organisms is programmed and co-ordinated by genes. No genes have been attributed deterministic role in survival span and genes never evolve to cause disadvantage to the organism [8]. Gene repair capacity is under both genetic as well as epigenetic control which does influence rate of aging. When genes encoding for molecules toward sustaining homeodynamics and homeostasis, cumulate damage and dysfunction, they become "virtual gerontogenes". Accumulating damages in form of mutations, epimutations, oxidation and aggregation of macromolecules are detrimental to longevity. Certain mutations accelerate aging changes, e.g. through altering insulin sensitivity and metabolism or dynamics of kinases, transcription factors and variety of biological pathways. Altered gene regulation, accumulation of somatic mutations, protein errors and modifications, imbalance of reactive oxygen species and free radicals, immune system deregulation and neuroendocrine dysfunction are involved in systemic homeodynamic failure. At the cellular level shortening of telomeres (the repeat neucliotide containing noncoding DNA at chromosomal ends that protect loss of important DNA), progressive demethylation in the DNA and consequent progressive compromise of renewal and repair system of cells are appealing mechanisms of aging.

Telomeres are DNA protein structures that form protective caps at ends of chromosomes providing safeguard from degradation and maintain genomic integrity. Telomerase enzyme adds DNA sequence repeats in telomere region at the end of chromosomes. Telomeres shorten with each cell division as process of aging. Accelerated loss of telomeres associates chronic age related diseases. Oxidative stress increases erosion of telomere length by oxidative modification of guanine in DNA at each cell division cycle in exposed cells. Shorter telomere length associates increase of body mass index and adiposity and age related pathologies [9]. While adiponectin correlates to longevity [10], disruptive leptin function results in metabolic decline and abnormal body fat distribution [11]. Fat plays important role in regulation of energy metabolism and immune responses. These effects are implemented through adipose tissue derived cytokines [12]. Gradual erosion of telomere length proportionately increase genetic instability over the life course. When critically short length is reached, cell stops dividing making no regenerative contribution to systemic maintenance [13].

Pathophysiologic understanding of the aging process

Ongoing biomedical research suggests disturbed rhythm of lifestyle eg., night shifts and stressors, improper and excess eating, physical inactivity as provocative to multifaceted molecular mechanisms hastening the process of ageing. The cellular senescence displays arrested division and threatened survival. Aging organism displays progressive compromise in physiological functions and inability for homeostasis in face of stress, with increased risk of age related diseases. Many aspects of physiology and behavior are driven by intrinsic circadian rhythm which keeps synchrony among varied biological processes of the organism and co-ordinates them with the environment. Components of the biological clock are also crucially involved in modulating physiological response to genotoxic stress (specially, the oxidative stress), regulation of cell cycle, other proageing mechanisms, carcinogenesis etc. Components of energy homeostasis, notably in the adipocytes, exhibit circadian rhythm in energy balance, feeding behavior and regulation of body weight [14]. Dysegulation of glucose and lipid metabolism, insulin sensitivity, detoxification of xenobiotics, and such other activities in varied permutations and combination, aggravating ageing changes [15]. Psychological stress denotes overwhelming demand for constant adjustments to changing environment and its molecular consequences (e.g. stress hormones, insulin sensitivity, oxidative stress, inflammation, etc.). It links to unhealthy aging process [16, 17].

Negative effects of major stress on health are well documented. The aspects of stress-resistance however, have potential to guide strategies for delaying ageing, especially at cellular level. Exposure to short term stress may strengthen cellular adaptive response to stress (hormetic stress) with enhanced activity of molecular chaperones and other defensive mechanisms. Prolonged exposure to stress, on the contrary, may overwhelm compensatory responses [18].

Ageing process: as mTOR driven

Among the earliest theories of ageing being driven by oxidative stress , presupposes intracellular nutrient and energy status as under constant scrutiny including, functional state of mitochondria and concentration of reactive oxygen species produced in them and co-ordinated flow of such information along diverse multiple

signaling pathways subserves regulation of life span. The concept now prevalent is that ageing is not simple result of molecular damage (nor by free radicals), but results from a purposeless quasi programme (programme like but not a programme), partly driven by TOR (target of rapamycin). TOR in eukaryotic cells is a conserved member of phosphatidylinositol kinase-related kinases family. In the mammals rapamycin sensitive is the mTOR Complex 1mTORC1. mTOR signaling pathway is master regulator of cell growth and metabolism [19]. The quasi-programmed phenomenon of ageing is driven by the over reaction of the crucial nutrient sensing mTOR (mammalian target of rapamycin) gero-gene. mTOR driven ageing may be triggered or accelerated by decline or loss of responsiveness to activation of another energy sensing protein AMPK (AMP Kinase). AMPK is a critical gero-suppressor of mTOR. The age related infirmity, therefore reflects synergistic interaction with our evolutionary path to sedentarism. Physical inactivity chronically increases a number of mTOR activating gero-promoters (e.g. Food, growth factors, cytokines, insulin). These lead to defective design of central metabolic integrators such as mTOR and AMPK [20]. mTOR kinase integrates signals from nutrients, energy status, growth factors and a variety of stressors. It then affects rate of protein synthesis and degradation via autophagy, through number of downstream effects [21]. mTOR mediates the switch between growth and somatic stability to extend lifespan.

Nutrients (glucose, amino acids, especially leucine) and fatty acids directly activate the mTOR pathway and also increase insulin levels, which can additionally activate mTOR [22]. Modulation of mTOR signaling network affects mRNA translation, transcription, autophagy, ribosomal biogenesis, metabolism and cell survival, proliferation, cell size and growth, endoplasmic reticulum stress signaling and other stress responses [23]. Constitutively active TORC1 augments overall protein synthesis by increasing the speed of ribosomal elongation along transcripts. Such elongation induces different extents of translational errors with wrong incorporation of amino acids and defective folding of polypeptides, resulting in failure of protein quality control [24]. Rapamycin can inhibit TORC1 and inhibit translational activity. This will reduce waste-full formation of rough proteins during cell division that can impair lifespan of non-dividing cells. Rapamycin inhibitory effect is mediated via ribosomal S6Kinases.

Hyperfunction theory of ageing postulates that proximal cause of ageing is not the accumulation of random molecular damage, but overactive cellular functions (25). The nutrient sensing TORC1 signalling pathway seems to be a key contributor. Its inhibition by drugs or dietary restriction reduces translation, apparently allowing for better protein quality control. Accumulation of protein misfolding is thus reduced, which would otherwise cause age related pathologies. Reduced protein translation has been linked to increased life span [26].

Inhibition of mTOR is major way to maintain proteome and manage energy through the aging process. When cell energy content falls, that activates AMPK.AMPK directly phosphorylates TSC2 (Tuberous Sclerosis Complex 2), a negative regulator of mTORC1 and Raptor, an essential binding partner for induction of translation by mTORC1, resulting in inhibition of laters activity. The mTORCI1, S6K and AMPK constitute a complex feedback loop that is sensitive to dietary restriction and can redirect growth, metabolism and lifespan. Besides nutrients and growth factors, inputs about environmental stressors also influence control of growth. Osmotic stress, hypoxia, endoplasmic reticulum(ER), stress, genotoxic stress, mechanical forces and contraction (muscle movement) may all regulate mTORC1 activity. The growth hormone/insulin like growth factor 1(GH/IGF1), axis is strongly implicated in diet restriction effect. Reduced GH and IGF1 signaling associates with longer lifespan. Dietary Restriction (DR) reduces GH/IGF1 pathway signaling. There is key role of energy efficiency in determining health and longevity. Equally importantly, modulation of mTOR activity mediates proteostasis [27].

Role of GCN2: General Control Non depressible Kinase 2(GCN2 kinase) is another nutrient sensing pathway. It phosphorylates elF2-alfa transcription factor following nutrient and other stress.GCN2 has central role in stress management by activating key transcription factors such as ATF4 and NFkB in mammals. This stress induced reprogramming also determines life span [28]. For resource conservation and homeostasis under stress, the typical response is inhibition of protein synthesis with reprogramming of gene expression [29]. Inhibition of protein synthesis is attained through phosphorylation of elF2- α, the translation initiator factor 2.GCN2 is the only elF2-alfa kinase conserved through evolution that responds to nutrient depletion by regulating amino acid transport and metabolism. Other stressors also activate GCN2. The kinase also regulates lipid metabolism, oxidative stress resistance, feeding behavior, NFkB signaling, synaptic plasticity and memory.

AMPK: The anti-ageing crusader:

Adenosine mono phosphate activated protein kinase AMPK has emerged as key nutrient-sensor, with ability to regulate whole body metabolism. AMPK is activated by fall in cellular ATP or energy status, indicated by

increased AMP/ATP ratio. Upon activation AMPK turns on, catabolic pathways to restore ATP levels. For the short time frame, glycolysis and fatty acid oxidation is promoted. For long time frame mitochondria content of cell and use of mitochondrial substrates as energy source are increased. Mitochondrial fitness is of great interest in ageing, as effective control of mitochondrial biogenesis, metabolism and turnover is crucial for healthy ageing [30].

AMPK activation is generally linked to the stimulation of metabolic responses in order to prevent metabolic and energy crisis, in situations where ATP synthesis is compromised. Such situations can be low nutrient availability and accelerated ATP consumption states, as exercise and fasting. Activated AMPK stimulates catabolic processes to generate ATP and inhibits ATP consuming anabolic processes that are not essential to immediate cell survival. The later include biosynthesis of fatty acids and sterols, cell growth and division. AMPK is final sensor for glucose and lipid metabolism and integrates nutritional and hormonal signals in peripheral tissue and the hypothalamus. It mediates regulation of food intake, body weight and glucose and lipid homeostasis [31].

mTOR/ ULK 1 Regulation

AMPK signaling is major inducer of autophagy associated with the reduction of energy metabolism, autophagy can be activated by several stressors and seems to be associated with stress resistance. AMPK can regulate initiation of autophagosome formation via different signaling mechanisms. mTOR, the conserved serine/threonine protein kinase is potent inhibitor of autophagy. mTOR is involved in the signaling pathways induced by growth factors, abundant nutrients and sufficient energy states. AMPK can inhibit activity of mTOR complex (mTORC1) via two different mechanisms. It may directly phosphorylate a regulatory component of TORC1, Raptor. It may phosphorylate also TSC2 protein which also suppresses mTOR activity [32, 33]. AMPK dissociates mTORC1 from ULK1 complex to positively regulate autophagy indirectly. Directly, AMPK may bind ULK1 complex and phosphorylate it to stimulate autophagy [34].

AMPK opposing effect of Insulin/IGF1 pathway, in respect to longevity

Insulin/IGF1 pathway also activates mTOR kinase and its downstream targets that regulate protein and ribosome synthesis. mTOR is detrimental as it accelerates ageing process by potent inhibition of autophagy. It is yet unsettled, if lifespan extension is conferred through activation of autophagy or by inhibition of other downstream targets of mTOR. A downstream target of insulin/IGF1-mTOR pathway, S6K1 kinase, can repress AMPK signaling. Deletion of S6K1 stimulates AMPK signaling allowing longevity promotion [35]. Insulin /IGF1 signalling associated with growth hormone regulation represents crucial somatotrophic axis in mammals. Kurosu et al. [36] demonstrated that over expression of klotho protein inhibited insulin/IGF1 signaling and increased life span. Functional deficiency of klotho enhanced premature ageing.

Insulin/IGF1 and AMPK signaling pathways are mutually inhibitory. Insulin/IGF1 pathway may inhibit many networking antiageing pathways of AMPK also. AMPK phosphorylates insulin receptor substrate 1 to inhibit insulin/IGF1 signalling [37]. AMPK however seems to enhance insulin/IGF1 signalling if that supports its metabolic function, e.g. glucose uptake, but represses energy consuming pathways.

AMPK activity is key for mitochondrial biogenesis, but declines with age. Another theory of ageing as consequent to decline in mitochondrial biogenesis is thus, promulgated. Multiple endogenous and exogenous factors regulate mitochondrial biogenesis through PPAR-gamma co-activator- 1alpha (PGC 1alpha). Activators of PGC-1alpha include nitric oxide, CREB (AMP response element binding protein) and AMPK. Activation of the AMPK pathway results in inhibition of the mTOR pathway, conferring possible longevity benefit.

Calorie restriction stimulates, while nutritional overload impairs AMPK activity and concurrently induces insulin resistance. New roles of AMPK beyond maintenance of energy metabolism during state of increased consumption have become known [20]. The rate of living theory of ageing emphasized that energy metabolism maintains homeostasis in the organism, whereas excessive energy consumption enhances ageing process. AMPK may co-ordinate preserving mechanisms as autophagy and increased stress resistance of tissue. AMPK upregulates thioredoxin expression to beat oxidative stress, and represses endoplasmic reticulum stress and inflammation. All these are antiageing in effect. AMPK responsiveness declines during ageing process leading to emergence of age related disorders. Age related changes in protein phosphatases may be basis for suppressed AMPK activation in ageing. Low grade inflammation of ageing also prominently impairs AMPK function.

Multiple networking pathways of lifespan regulation

Ageing research reveals several signaling pathways simultaneously engaging for regulating aging and affecting lifespan. They are organized in integrated network, which has positive feedback effect on AMPK activity.

CTRCs (CREB-regulated transcription co-activator 1), are coactivators of CREB mediated gene transcription and are targets of AMPK action. Inhibition of CRTC induced CREB activation is crucial regulator of ageing and longevity.

AMPK and SIRT1 (silent information regulators) signaling pathways are evolutionally conserved energy sensors in cells responding to the increase in cellular AMP and NAD+ concentrations respectively(38). SIRT1 is major regulator of cellular energy metabolism and many components of cell survival, e.g. apoptosis, cell proliferation and inflammation. SIRT1 regulates stress resistance by directly modulating function of FaxO, p53 and NFkB signaling. The activation of AMPK stimulates functional activity of SIRT1 by increasing intracellular NAD+ concentration [39].

FaxO axis: the fork head transcription factors are involved in regulation of apoptosis, cell cycle, stress resistance, glucose and lipid metabolism and inflammation. The target genes of AMPK-FaxO3 pathway associated with longevity include those involved in defense against oxidative stress and DNA repair. The FaxO factors are integral to other longevity mechanisms as, inhibition of NFkB and age related inflammation. Stimulation of autophagy occurs both through FaxO andULK1/mTOR pathways.

FaxO factors and p53 exhist in complex interaction networks.p53 is one target protein of AMPK for control of expression as well as transactivation. Arf/p53 pathway activation promotes longevity via increased expression of antioxidant genes and autophagy. Mitochondria are major targets of several p53 actions which foster their integrity.

AMPK activation can inhibit signaling of master regulator transcription factors of inflammation [40]. AMPK-SIRT1-NFkB signaling pathway has major implication in controlling immune function. AMPK can stimulate Nrf2/SKN 1 signalling which acts in concert with the function of AMPK-FaxO3a axis in the generation of oxidation stress resistant phenotype of long lived animals.

Biomedical contemplation on interventions for control of Life span:

Autophagy is process of lysosome dependant intracellular recycling amino acids and energy resource particularly important in stress. Autophagy, insulin/IGF1 signaling, dietary restriction and reduced mitochondrial function, can modulate the proteostatic machinery to maintain stability of proteome. These mechanisms provide targets for therapeutic intervention [41]. Reducing insulin/IGF1 signaling is prime aging regulatory pathway, effected by protection against toxic protein aggregates in models of Alzheimers disease.

Pharmacologically upregulated autophagy increases clearance of toxic intracellular waste and enhanced lifespan. An understanding on regulatory signals of autophagy however bears serious gaps [42]. Deregulation of mTOR pathway is implicated in age associated disorders and mTOR inhibitor rapamycin treatment offers some curb, with scope for developments in multimodal combination regimens [19].

Pathways sensitive to dietary nutrients can be targeted to alter lifespan include, mTOR pathway, AMPK pathway, oxidative stress response through SRN1/Nrf2. Protein quality control through increased autophagy and general (hermetic) stress response.

Benefit of Weight Reduction: Under calorie restriction more body fat is lost influencing factors at interface of metabolism and inflammation [43]. Calorie restriction in aging rat improves carbohydrate metabolism by decreasing visceral fat and increasing insulin sensitivity [44]. Interventions that stimulate metabolism and/or activate white adipose tissue signaling mimick calorie restriction. Rapamycin is approved classical TOR-inhibitory agent with diverse potentials of imparting longevity. mTORC1 plays central role via S6K and 4E BP [45], that leads to decreasing over all translation allowing better fidelity of autophagy and mechanisms degrading misfolded and damaged proteins. Anti-inflammatory effect of rapamycin and role in depletion of small molecules such as endocannabinoids may also be relevant. Many clinically employed compounds, e.g. aspirin, reduce MTORC1 activity and also activate AMPK. Perhexiline, niclosamide, rottlerin and amiodarone also inhibit mTORC1, as does natural product phenylethyl isothiocynate (in brassicaceae vegetables).Many mTOR inhibitory drugs may target insulin/IGF1 signaling, pathway to increase lifespan.

AMPK Activation:

Mitochondrial dysfunction is an important component of age related diseases, e.g. type 2 diabetes, Alzheimers etc. AMPK acts as an energy sensor of cell and works as key regulator of mitochondrial biogenesis. Number of drugs and hormones directly or indirectly activate AMPK. Therapeutic exploration is however limited to only metformin that activates AMPK and suppresses mTOR, both life extending actions [46]. Many longevity genes are clustered in to nutrient sensing and metabolic adaptation pathways.

Hormetic stress response induction/preconditioning (47)

Adaptation and survival of cells and organism requires ability to sense proteotoxic insults and to co-ordinate protective cellular stress response pathways and chaperone networks related to protein quality control and stability. The toxic effects that stem from the misassembly or aggregation of peptides/proteins in cell are collectively termed proteotoxicity and result in metabolic, degenerative and neoplastic pathologies.

Strong interest lies in discovery of agents capable of inducing beneficial cytoprotective heat shock response and resistance against major stress. Low dose "HORMETIC" stress pathways include signaling mechanisms by which the carnitine system, mitochondrial energetics and activation of critical vitagenes, modulate signal transduction cascades conferring cytoprotection.

Modest free radical stress and lipid peroxidation products induce hermetic stimulation of energy metabolism pathways, mitochondrial biogenesis and upregulation of protein chaperones and antioxidant systems [48].

Protein thiols regulating cellular redox state are crucial mediator of multiple metabolic signaling and transcriptional processes. Pro-survival pathways are activated by vitagenes producing Hsps, glutathione, bilirubin with antioxidant and antiapoptotic property. Drugs capable of inducing Hsp response are of great interest, therefore.

SIRT1 deacetylates and activates transcription regulator PGC1-alfa that directs adaptive response to caloric restriction and exercise, promoting production of antioxidant and detoxifying enzymes. Heat Shock transcription factor 1(HSF1) is central regulator of gene expression of Hsps and other vitagenes in electrophile counterattack response (against reactive oxygen species and radicals). The vitagenes expression of this group is regulated by Keilch-like ECH-associated protein 1 Keap1/Nrf2 /ARE (antioxidant response element) pathway [49].

Variety of natural chemicals are inducers of Keap1/Nrf2/ARE pathway. Their common shared property is reactivity with sulfhydryl groups.

Hormetic mechanisms account for health benefits of phytochemicals. They generally activate adaptive cellular response pathways including kinases, and transcription factors that induce the expression of genes encoding antioxidant enzymes, protein chaperones, phase-2 enzymes, neurotrophic factors and other cytoprotective proteins. Sulforaphane (Brassicaceae), curcumin and resveratrol are inducers of Keap1/Nrf2/ARE pathway. Resveratrol also activates Sirtuin/FOXO pathway with increased antioxidant enzymes and survival protein buildup [50]. Other phytochemicals may activate hermetic transcription factors CREB (cyclic AMP response Element Binding protein) leading to induction of genes coding growth factors and antiapoptotic proteins [51].

Carnitine and Acetyl Carnitine: Mitochondrial content of endogenous acetyl carnitine is indicator of mitochondrial metabolism of acetyl CoA. Acetyl CoA acts on the acetylation status of mitochondrial proteins that increase mitochondrial transcription and protein synthesis. As a result, cytochrome B content increases with consequent increase in electron transport chain activity and stimulation of oxidative phosphorylation. Supplement should potentially restore aging related mitochondrial defect, therefore [52]. Acetyl carnitine (ALC) upregulated Hsps and expression of redox sensitive transcription factor Nrf2 following the hormetic low dose effect [53]. The evidence for modulation of mitochondrial biogenesis via transcriptional control of nuclear-respiratory factor NRF1 [54], highlight role of carnitine system in mitochondrial metabolism.

Carnitine system functions as vitagene prototype for processes of cell survival that require energy for cellular stress response and redox homeostasis [55].

Redox Biology Paradigm

As per redox biology paradigm, antioxidants primarily serve to modulate complex networks controlling cell signaling and metabolism. Central idea is that redox active mediators,eg nitric oxide, hydrogen peroxide and lipid radicals act as site specific mediators of cell signaling, protein cystein residues are the sensors or receptors of these different redox mediators AND the" traditional" antioxidants, e.g. glutathione, α-tocopherol serve the essential functions of insulating distinct redox signaling domains in the cell from cross-talk.

Dysregulation of these pathways would influence metabolism, autophagy, cell growth and repair. Most successful translational use of these pathways is of course, the selective activation of Keap1/Nrf2 system, sure to yield new drugs. Lifespan enhancing metformin effect is also dependant on oxidative stress transcription factor Nrf2 [56]. Mechanisms of hormetic triggering of endogenous cellular defense pathways include, sirtuins and Nrf2 and related pathways that integrate adaptive stress. Emerging role of nitric oxide, carbon monoxide and Hydrogen sulphide gases in hormesis based neuroprotection and their relation to radical dynamics in membrane and redox signaling is drawing perticular research attention [57].

CONCLUSION AND PROSPECTS

Modern technical advances applied in aging research span across, nanotechnology, bioinformatics, single cell analysis, molecular heterogeneity analysis, analyses of epigenetic regulators of stress, analysis of post synthetic modification of biomolecules etc. Scientific gerontology, envisages rational steps to slow down aging process and rejuvenate physiological function. Redesigning of structural and functional units of body by manipulations at level of genes, gene products, macromolecular interactions, interaction with the milieu etc. are being worked upon. Their practical application in checking or reversing aging changes, is currently, far too distant.

Biochemical interactions and tradeoffs between stressor and biologic cellular responses, including pleotropic effects require thorough learning. A range of usable physical, chemical or biological stressor options with feasible technology for application must become available and must also conform to safety and efficacy standards like drugs. The task of advancing hormesis principle for practical use requires competent calibration and monitoring of magnitudes appropriate for different stressor interventions and ways to monitor them, including need for defining optimal stressor dose for given stage of aging process. Bioactive constituents from plant food have shown novel modulatory potential for transcription phenomena [58]. Since redox regulation and transcription factor cystein modification are central to both Keap1/Nrf2/ARE pathway and the Heat shock response, such multi target agents, all of which are reactive with sulfhydryl groups, are ideal for simultaneously manipulating ageing pathways to achieve synergistic benefits. Exploiting the ability of small molecules, many of them from diet and safe, to stimulate defensive stress response is highly aspired, and the ultimate objective ought be adding life to years rather than years to life [59].

Conflict of interest statement

There is no conflict of interest among the authors.

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Results of Gastroesophageal Collector Total Dissociation in Patients with Portal Hypertension

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ABSTRACT: The purpose of research was to study long-term results of the modified technique of gastroesophageal collector total dissociation (GECTD) in patients with portal hypertension. Materials and methods. Currently a modified version of the operation has been performed in 73 patients with the portal hypertension (PH) syndrome. In 36 patients the cause of PH was liver cirrhosis, 30 patients were diagnosed with extrahepatic form of PH, mixed form of PH was determined in 8 patients. The age of patients ranged from 13 to 65 years, thus the median was 31.6 ± 1.7 years. Patients randomizing by gender was as follows: men - 44, women - 29. In 53 cases patients were admitted in a planned order, and 20 patients were delivered urgently with the clinical picture of gastroesophageal bleeding. Results and discussion remote period was followed up in 46 patients with primary procedure and in 66 patients with a modified technique of GECTD. Rebleeding was observed in 15.2% of patients, 6.5% on the background of anastomositis. Gastrostasis occurrence was detected in 3 of 46 patients. Liver failure occurred in 23.9% of patients, 15.2% patients died on the background of these complications. In the group with a modified procedure bleeding was observed in 6.0% cases. Bleedings from erosion in the area of ligature transection were stopped conservatively. Mortality in long-term period of observation was 7.6% (5 patients). Overall mortality for the near and distant periods in the comparison groups was 22.2% and 16.4%, respectively. Conclusion –dissociation of gastroesophageal venous reservoir by ligature transection on synthetic prosthesis, unlike previously proposed methods of GECTD allows not only to ease technique of operation, but also provides prevention of early postoperative complications associated with traumatism of previous methods, as well as the stomach gross functional disorders in the long term period.

Author Keywords: Liver Cirrhosis, Portal Hypertension, Dissociative Operations, Technique of Ligature Transection, Bleeding from Esophageal Varices

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INTRODUCTION

Among all gastrointestinal hemorrhages from esophageal varices in patients suffering from liver cirrhosis (LC) with portal hypertension (PH) are distinguished by specific severity of clinical presentations, serious complications and high probability of lethal outcome. Without indications to radical cure of LC – liver transplantation, the basic direction of surgical treatment for such patients is of portal pool vessels reconstruction [1-3]. But there are particular indications for portosystemic shunting and it is a big patients group among those in which such intervention is impossible because of some reasons and it is required to perform another type of surgical treatment. Among mentioned portoasigos dissociation surgeries remain as a method of choice. The main advantages of them are maintenance of constant liver portal perfusion, absence of post-shunting encephalopathy and wider facilities at performing in emergency surgery of esophageal bleedings [4-6]. Besides there is strategic deficiency in emergency and planned dissociative operation types and a lack of stable late fates. So, after a year or less active restoration of varices with increasing risk of bleeding recurrence has place [7-9]. The worked-out and adopted into practice original techs of gastroesophageal collector total dissociation (GECTD) in RSCS named after acad. V.Vakhidov, have high hemostatic efficiency and are directed on elimination of known surgeries

defects. The analysis of long-term results of these surgeries with the estimation of their prophylaxis efficiency of esophageal bleedings and patients survivability presents particular interest.

Original method of GECTD with ligature transection of subcardinal part of stomach with following forming of gastrogastal collateral anastomosis has been initially worked out (such surgeries has been performed in 63 patients from 1998 to 2007). Surgery stages have included: stomach mobilization through greater stomach transaction by ligature type at the subcardinal part level; forming of gastrogastal collateral anastomosis above the ligature. Such type of surgery has two variants of performing: using ligatures or steplers. By gaining an experience we came to conclusion that a ligature type is more preferable [7, 10].

Analysis of long-term results (from 3 months to 10 years) of performed dissociative operations has been carried out in 46 patients. Rebleeding has been registered in 10.9% patients, and in 6,5% cases on the background of anastomositis. Occurrence of gastrostasis have been revealed in 5 of 46 patients. Control endoscopy 3 months after surgery has revealed stomach recanalization in the area of ligature transection with forming of two ways for food passage – recanalized natural one and through gastrogastal anastomosis. 19.6% patients died on the background of complications. Mentioned facts allowed to suppose a probability of performing ligature transection of stomach subcardinal part on wireframe base with the saving of natural way for food passage without gastrogastal anastomosis.

MATERIAL AND METHODS

GECTD modified method (F.G. Nazirov's operation) was adopted in clinical practice in 2008 [10]. Distinctive feature of new method was that dissociation is achieved because of use intraluminal prosthesis installed during the surgery.

Method is carried out as follows: approach – upper-midline laparotomy. Proximal devascularization of stomach up to esophagus abdominal part through greater and lesser curvature is carried out. Organ blood flow is saved through right gastric and two gastroepiploic arteries. The left gastric artery is ligated and transected. All short vessels of stomach are also ligated and transected (Figure 1). Then transversal gastrotomy is carried out in medium part of stomach body along anterior wall and through a formed hole synthetic prosthesis is introduced into stomach lumen and is located in the lumen of stomach subcardinal part. Above the prosthesis introduced into stomach lumen, over serous membrane ligature is put in which divides stomach to upper 1/3 and lower 2/3 parts. Ligature is tightened over the prosthesis and at the same time the prosthesis is fixed by surgeon's finger introduced into its lumen. So, the prosthesis location and ligature's tension is controlled. Then repeated ligature is put in over the first one. Corrugation of the prosthesis provides ligatures' fixation preventing their displacement (Figure 2). Nasogastric probe is passed through the prosthesis with the aim of decompression in the postoperative period. Gastrotomic hole is sutured by double-row suture. A number of sero-serous sutures are also pit in over stomach ligature. Pyloroplasty is carried out additionally.

Endoscopic investigation is performed after 1-1.5 month and the prosthesis is removed out of stomach lumen. By this time put in ligatures over it are penetrated into stomach lumen and venous reservoir is dissociated.

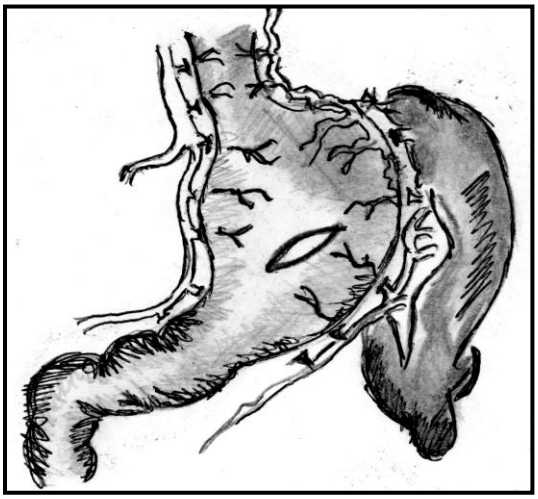

Figure 1. Stage of stomach and esophagus abdominal part devascularization with gastrotomy.

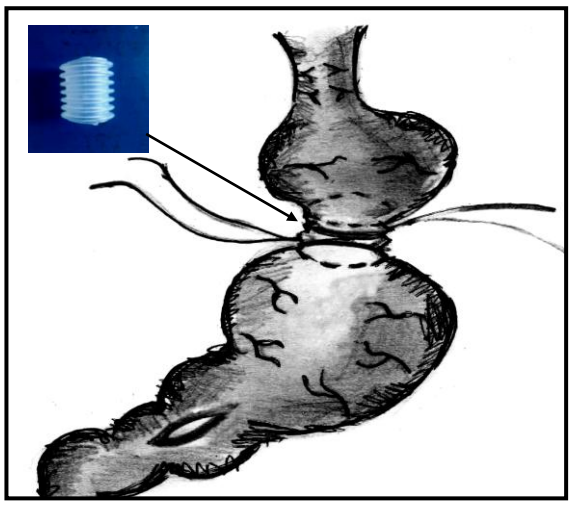

Figure 2. Stage of ligature transection on the ring- prosthesis.

Currently operation has been performed in 73 patients with PH syndrome. In 36 patients the cause of PH was LC, in 30 patients it has been diagnosed a hepatic form of PH and in 8 cases a combined form of PH has been determined. Patients age has been varied from 13 to 65 years, thus the median was 31.6 ± 1.7 years. Patients randomizing by gender was as follows: men - 44, women – 29. In 53 cases patients were admitted in a planned order, and 20 patients were delivered urgently with the clinical picture of gastroesophageal bleeding. Patients were underwent both general (clinical and biochemical blood tests, ECG, chest X-ray) and special (liver radioisotopic investigation, angiographic) investigation methods.

The grade of esophageal varices is estimated by Shertsinger's classification [11]. The second grade of esophageal varices has been revealed in all patients. All patients had esophagogastric bleeding in anamnesis and 40 (54.8%) of them - many times. In 13 cases patients additionally have been undergone splenectomy. In 8 (11.0%) patients at admission diabetes mellitus has been revealed.

RESULTS

At the nearest postoperative period the most frequent complication of earlier worked out dissociative methods were cardiofundal anastomosis insufficiency (11.7% - at planned surgeries and 21.1% - at emergency interventions). Unlike them, an offered new method is carried out through small gastrotomic hole and such complications has not been observed. From other side in more 11.1% patients anastomositis development has been noted which significantly increased the risk of bleeding development from anastomosis zones. Hepatic failure and encephalopathy have been noted in 15 (23.8%) patients. General lethality in the nearest period made up 11.1% (7 patients).

Modified ligature transection allowed to level completely the risk of anastomosis failure and to reduce a frequency of hepatic failure and lethality (Table 1). Radiologic-contrast investigation 10 days after surgery showed that prosthesis is freely passable; stomach evacuation functions failure has not been observed. One month after surgery at control endoscopic investigation a synthetic cylinder was removed without technical difficulties. Regress of esophageal varices has been noted in all cases.

Table 1. Comparative frequency of early postoperative complications in patients with GECTD by different methods

Complications	Original method	Modified method
Anastomosis failure	7 (11.1%)	--
Stomach wall necrosis in ligature transection area	2 (3.2%)	2 (2.7%)
Hepatic failure	15 (23.8%)	12 (16.4%)
Lethality	7 (11.1%)	7 (9.6%)

The analysis showed that predisposing factor to stomach wall evident ischemia development with necrosis probability in ligature area and above prosthesis is because of presence of concomitant diabetes in patients. Performing stomach devascularization with following ligature transection on the background of diabetic angiopathy significantly disturbs organ's trophics and it was a cause of necrosis. At the absence of diabetes mellitus we did not observe such type of complications. In comparative aspect the risk of stomach necrosis in the area of transection at diabetes mellitus presence increased up to 25% (in 2 from 8 patients with diabetis). This fact has influenced to technical aspects of performing dissociative operations in patients with decompensated stage of diabetes. Currently a surgery is limited only by stomach devascularization with additional ligation of left gastric vein as basic afflux to gastroesophageal venous reservoir at PH.

Remote period has been observed in 46 patients with primary procedure and in 66 patients with a modified technique of GECTD. Rebleeding was observed in 15.2% of patients, and 6.5% on the background of anastomositis. Gastrostasis occurrence was detected in 3 of 46 patients. The phenomena of liver failure occurred in 23.9% of patients. 15.2% patients died on the background of these complications (Table 2). In the group with a modified procedure bleeding was observed in 6.0% cases. Two patients with bleeding from esophagus lower one third were successfully underwent sclerotherapy and there was not noted a following recurrence. Bleedings from erosion in the area of ligature transection were stopped conservatively. Mortality in long-term period of observation was 7.6% (5 patients). Overall mortality for the near and distant periods in the comparison groups was 22.2% and 16.4%, respectively.

Table 2. Comparative frequency of complications after GECTD in remote period

Complications	Original method	Modified method
Bleeding from esophageal varices	4 (8.7%)	2 (3.0%)
Bleeding from anastomosis area (anastomositis) or ligature transection	3 (6.5%)	2 (3.0%)
Gastrostasis	3 (6.5%)	1 (1.5%)
Hepatic failure	11 (23.9%)	8 (12.1%)
Mortality	7 (15.2%)	5 (7.6%)
Overall mortality in 12 months period	14 (22.2%)	12 (16.4%)

Advantages of GECTD modified method are: refusal from performing cardiofundus anastomosis – natural tract trough stomach by means of prosthesis fixed in cardinal part is saved; reduction of surgery duration due to performing gastrotomy without cardiofundal anastomosis; decrease of the risk of gastrotomic hole failure development – the length of gastrotomy is 3 cm, absence of cardiofundal anastomosis; broad intramural zone of stomach cardinal part veins dissociation – external application of two ligatures above prosthesis introduced into stomach cardinal part creates the length of sclerosis up to 1 cm.

Analysis of patients survivability with LC and PH after GECTD showed that the lowest index has been revealed in the groups with large nodular cirrhotic transformation (survivability median – 24 months), in patients with bleeding in anamnesis (survivability median – 36 months) and with decompensation by edematous ascitic syndrome before operative intervention (survivability median – 12 months). Investigation has shown performing GECTD to patients with LC and high portal pressure increases the risk of hemorrhagic complications development in early and late postoperative period and respectively decreases survivability indexes till 1 year observation to 62%, 3 years – up to 47% and it is connected not only with hypertension but also with forced technical aspects of surgery (ligature transection and gastrogastra-anastomosis) on the background of portal gastropathy.

Performing GECTD to patients with LC on the background of edematic-ascitic syndrome decreases survivability indexes in the period of observation till 1 year up to 48%, 3 years – up to 43% and it is connected with progressing of two main factors in remote period – portal hypertension and increasing hepatic failure with functional decompensation of hepatocytes.

GECTD in patients without vascular and edematic-ascitic decompensation of LC with PH increases survivability indexes in the period of observation till 1 year up to 87%, 3 years – up to 67% and 5 years up to 58%. In other cases on the background of progressing above mentioned complications, it is reasonable to perform different types of intersystem vascular bypass as basic type of intervention directed to portal system decompression.

CONCLUSIONS

Dissociation of gastroesophageal venous reservoir by ligature transection on synthetic prosthesis previously implanted in stomach unlike previously proposed methods of GECTD allows not only to ease the technique of operation, but also provides prevention of early postoperative complications associated with traumatism of previous methods, as well as the stomach gross functional disorders in the long term period.

Advanced original tech of GECTD is the most perspective operative method in emergency surgery and in planned operative interventions in patients with PH syndrome undergone repeated operative treatment or it can be alternative to portosystemic shunting method, at impossibility of performing the last one. Our investigation shows that described technique had showed it reliability and efficiency.

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Competing interests

The authors declare that they have no competing interests.

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Acceptable Examples (at References section)

For Journals:
1. Hasan V, Sri Widodo M and Semedi B. 2015. Oocyte diameter distribution and fecundity of Javaen Barb (*Systomus Orphoides*) at the start of rainy season in Lenteng River, East Java, Indonesia insurance. J. Life Sci Biomed, 5(2): 39-42.
2. Karen KS, Otto CM. 2007. Pregnancy in women with valvular heart disease. Heart. 2007 May; 93(5): 552–558.
3. Doll MA, Salazar-González RA, Bodduluri S, Hein DW. Arylamine N-acetyltransferase 2 genotype-dependent N-acetylation of isoniazid in cryopreserved human hepatocytes. Acta Pharm Sin B, 2017; 7(4):517-522.

For In press manuscripts (maximum 2):
Hasan V, Sri Widodo M and Semedi B. 2015. Oocyte Diamater Distribution and Fecundity of Javaen Barb (Systomus Orphoides) at the Start of Rainy Season in Lenteng River, East Java, Indonesia insurance. In press.

For symposia reports and abstracts:
Cruz EM, Almatar S, Aludul EK and Al-Yaqout A. 2000. Preliminary Studies on the Performance and Feeding Behaviour of Silver Pomfret (Pampus argentens euphrasen) Fingerlings fed with Commercial Feed and Reared in Fibreglass Tanks. Asian Fisheries Society Manila, Philippine 13: 191-199.

For Conference:
Skinner J, Fleener B and Rinchiuso M. 2003. Examining the Relationship between Supervisors and Subordinate Feeling of Empowerment with LMX as A Possible Moderator. 24th Annual Conference for Industrial Organizational Behavior.

For Book:
Russell, Findlay E, 1983. Snake Venom Poisoning, 163, Great Neck, NY: Scholium International. ISBN 0-87936-015-1.

For Web Site:
Bhatti SA and Firkins JT. 2008. http://www.ohioline.osu.edu/sc1156_27.hmtl.

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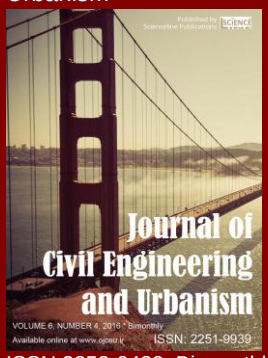

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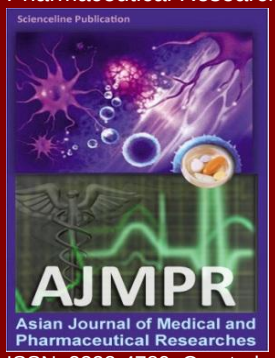

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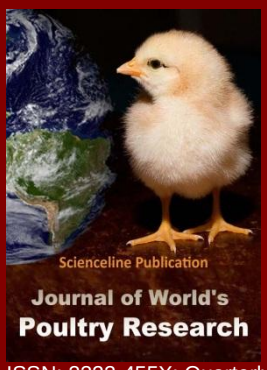

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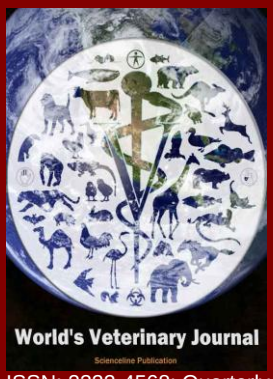

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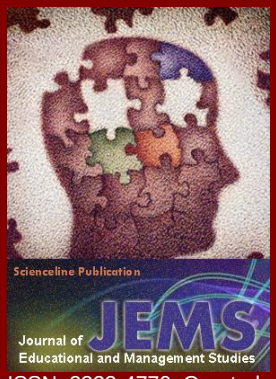

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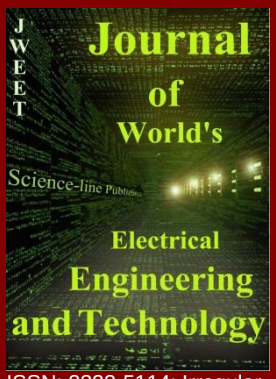

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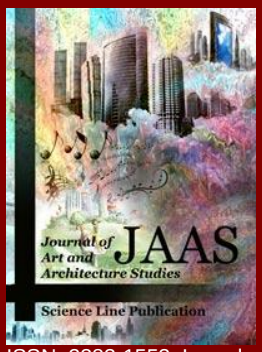

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